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(54) Title: QUINAZOLINE DERIVATIVES

(57) Abstract: The invention concerns quinazoline derivatives of Formula (I) wherein each of m, R¹, n, R² and R³ have any of the meanings defined in the description; processes for their preparation, pharmaceutical compositions containing them and their use in the manufacture of a medicament for use as an anti-invasive agent in the containment and/or treatment of solid tumour disease.

QUINAZOLINE DERIVATIVES

The invention concerns certain novel quinazoline derivatives, or pharmaceutically-acceptable salts thereof, which possess anti-tumour activity and are accordingly useful in methods of treatment of the human or animal body. The invention also concerns processes for the manufacture of said quinazoline derivatives, to pharmaceutical compositions containing them and to their use in therapeutic methods, for example in the manufacture of medicaments for use in the prevention or treatment of solid tumour disease in a warm-blooded animal such as man.

Many of the current treatment regimes for cell proliferation diseases such as psoriasis and cancer utilise compounds which inhibit DNA synthesis. Such compounds are toxic to cells generally but their toxic effect on rapidly dividing cells such as tumour cells can be beneficial. Alternative approaches to anti-tumour agents which act by mechanisms other than the inhibition of DNA synthesis have the potential to display enhanced selectivity of action.

In recent years it has been discovered that a cell may become cancerous by virtue of the transformation of a portion of its DNA into an oncogene i.e. a gene which, on activation, leads to the formation of malignant tumour cells (Bradshaw, Mutagenesis, 1986, 1, 91). Several such oncogenes give rise to the production of peptides which are receptors for growth factors. Activation of the growth factor receptor complex subsequently leads to an increase in cell proliferation. It is known, for example, that several oncogenes encode tyrosine kinase enzymes and that certain growth factor receptors are also tyrosine kinase enzymes (Yarden *et al.*, Ann. Rev. Biochem., 1988, 57, 443; Larsen *et al.*, Ann. Reports in Med. Chem., 1989, Chpt. 13). The first group of tyrosine kinases to be identified arose from such viral oncogenes, for example pp60^{v-Src} tyrosine kinase (otherwise known as v-Src), and the corresponding tyrosine kinases in normal cells, for example pp60^{c-Src} tyrosine kinase (otherwise known as c-Src).

Receptor tyrosine kinases are important in the transmission of biochemical signals which initiate cell replication. They are large enzymes which span the cell membrane and possess an extracellular binding domain for growth factors such as epidermal growth factor (EGF) and an intracellular portion which functions as a kinase to phosphorylate tyrosine amino acids in proteins and hence to influence cell proliferation. Various classes of receptor tyrosine kinases are known (Wilks, Advances in Cancer Research, 1993, 60, 43-73) based on families of growth factors which bind to different receptor tyrosine kinases. The classification

includes Class I receptor tyrosine kinases comprising the EGF family of receptor tyrosine kinases such as the EGF, TGF α , Neu and erbB receptors, Class II receptor tyrosine kinases comprising the insulin family of receptor tyrosine kinases such as the insulin and IGFI receptors and insulin-related receptor (IRR) and Class III receptor tyrosine kinases comprising the platelet-derived growth factor (PDGF) family of receptor tyrosine kinases such as the PDGF α , PDGF β and colony-stimulating factor 1 (CSF1) receptors.

It is also known that certain tyrosine kinases belong to the class of non-receptor tyrosine kinases which are located intracellularly and are involved in the transmission of biochemical signals such as those that influence tumour cell motility, dissemination and invasiveness and subsequently metastatic tumour growth (Ullrich *et al.*, Cell, 1990, 61, 203-212, Bolen *et al.*, FASEB J., 1992, 6, 3403-3409, Brickell *et al.*, Critical Reviews in Oncogenesis, 1992, 3, 401-406, Bohlen *et al.*, Oncogene, 1993, 8, 2025-2031, Courtneidge *et al.*, Semin. Cancer Biol., 1994, 5, 239-246, Lauffenburger *et al.*, Cell, 1996, 84, 359-369, Hanks *et al.*, BioEssays, 1996, 19, 137-145, Parsons *et al.*, Current Opinion in Cell Biology, 1997, 9, 187-192, Brown *et al.*, Biochimica et Biophysica Acta, 1996, 1287, 121-149 and Schlaepfer *et al.*, Progress in Biophysics and Molecular Biology, 1999, 71, 435-478). Various classes of non-receptor tyrosine kinases are known including the Src family such as the Src, Lyn and Yes tyrosine kinases, the Abl family such as Abl and Arg and the Jak family such as Jak 1 and Tyk 2.

It is known that the Src family of non-receptor tyrosine kinases are highly regulated in normal cells and in the absence of extracellular stimuli are maintained in an inactive conformation. However, some Src family members, for example c-Src tyrosine kinase, is frequently significantly activated (when compared to normal cell levels) in common human cancers such as gastrointestinal cancer, for example colon, rectal and stomach cancer (Cartwright *et al.*, Proc. Natl. Acad. Sci. USA, 1990, 87, 558-562 and Mao *et al.*, Oncogene, 1997, 15, 3083-3090), and breast cancer (Muthuswamy *et al.*, Oncogene, 1995, 11, 1801-1810). The Src family of non-receptor tyrosine kinases has also been located in other common human cancers such as non-small cell lung cancers (NSCLCs) including adenocarcinomas and squamous cell cancer of the lung (Mazurenko *et al.*, European Journal of Cancer, 1992, 28, 372-7), bladder cancer (Fanning *et al.*, Cancer Research, 1992, 52, 1457-62), oesophageal cancer (Jankowski *et al.*, Gut, 1992, 33, 1033-8), cancer of the prostate, ovarian cancer (Wiener *et al.*, Clin. Cancer Research, 1999, 5, 2164-70) and pancreatic cancer

(Lutz *et al.*, Biochem. and Biophys. Res. Comm., 1998, 243, 503-8). As further human tumour tissues are tested for the Src family of non-receptor tyrosine kinases it is expected that its widespread prevalence will be established.

It is further known that the predominant role of c-Src non-receptor tyrosine kinase is to regulate the assembly of focal adhesion complexes through interaction with a number of cytoplasmic proteins including, for example, focal adhesion kinase and paxillin. In addition c-Src is coupled to signalling pathways that regulate the actin cytoskeleton which facilitates cell motility. Likewise, important roles are played by the c-Src, c-Yes and c-Fyn non-receptor tyrosine kinases in integrin mediated signalling and in disrupting cadherin-dependent cell-cell junctions (Owens *et al.*, Molecular Biology of the Cell, 2000, 11, 51-64 and Klinghoffer *et al.*, EMBO Journal, 1999, 18, 2459-2471). Cellular motility is necessarily required for a localised tumour to progress through the stages of dissemination into the blood stream, invasion of other tissues and initiation of metastatic tumour growth. For example, colon tumour progression from localised to disseminated, invasive metastatic disease has been correlated with c-Src non-receptor tyrosine kinase activity (Brunton *et al.*, Oncogene, 1997, 14, 283-293, Fincham *et al.*, EMBO J, 1998, 17, 81-92 and Verbeek *et al.*, Exp. Cell Research, 1999, 248, 531-537).

Accordingly it has been recognised that an inhibitor of such non-receptor tyrosine kinases should be of value as a selective inhibitor of the motility of tumour cells and as a selective inhibitor of the dissemination and invasiveness of mammalian cancer cells leading to inhibition of metastatic tumour growth. In particular an inhibitor of such non-receptor tyrosine kinases should be of value as an anti-invasive agent for use in the containment and/or treatment of solid tumour disease.

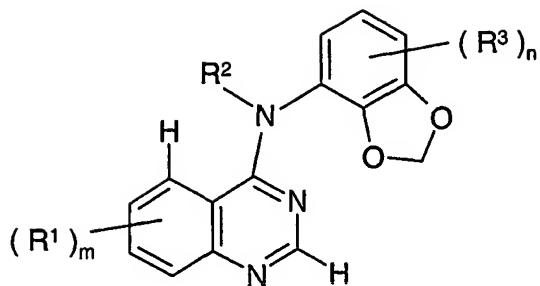
We have now found that surprisingly certain quinazoline derivatives possess potent anti-tumour activity. Without wishing to imply that the compounds disclosed in the present invention possess pharmacological activity only by virtue of an effect on a single biological process, it is believed that the compounds provide an anti-tumour effect by way of inhibition of one or more of the non-receptor tyrosine-specific protein kinases that are involved in the signal transduction steps which lead to the invasiveness and migratory ability of metastasising tumour cells. In particular, it is believed that the compounds of the present invention provide an anti-tumour effect by way of inhibition of the Src family of non-receptor tyrosine kinases, for example by inhibition of one or more of c-Src, c-Yes and c-Fyn.

It is also known that c-Src non-receptor tyrosine kinase enzyme is involved in the control of osteoclast-driven bone resorption (Soriano *et al.*, Cell, 1991, 64, 693-702; Boyce *et al.*, J. Clin. Invest., 1992, 90, 1622-1627; Yoneda *et al.*, J. Clin. Invest., 1993, 91, 2791-2795 and Missbach *et al.*, Bone, 1999, 24, 437-49). An inhibitor of c-Src non-receptor tyrosine kinase is therefore of value in the prevention and treatment of bone diseases such as 5 osteoporosis, Paget's disease, metastatic disease in bone and tumour-induced hypercalcaemia.

The compounds of the present invention are also useful in inhibiting the uncontrolled cellular proliferation which arises from various non-malignant diseases such as inflammatory 10 diseases (for example rheumatoid arthritis and inflammatory bowel disease), fibrotic diseases (for example hepatic cirrhosis and lung fibrosis), glomerulonephritis, multiple sclerosis, psoriasis, hypersensitivity reactions of the skin, blood vessel diseases (for example atherosclerosis and restenosis), allergic asthma, insulin-dependent diabetes, diabetic retinopathy and diabetic nephropathy.

15 Generally the compounds of the present invention possess potent inhibitory activity against the Src family of non-receptor tyrosine kinases, for example by inhibition of c-Src and/or c-Yes, whilst possessing less potent inhibitory activity against other tyrosine kinase enzymes such as the receptor tyrosine kinases, for example EGF receptor tyrosine kinase and/or VEGF receptor tyrosine kinase. Furthermore, certain compounds of the present 20 invention possess substantially better potency against the Src family of non-receptor tyrosine kinases, for example c-Src and/or c-Yes, than against VEGF receptor tyrosine kinase. Such compounds possess sufficient potency against the Src family of non-receptor tyrosine kinases, for example c-Src and/or c-Yes, that they may be used in an amount sufficient to inhibit, for example, c-Src and/or c-Yes whilst demonstrating little activity against VEGF receptor 25 tyrosine kinase.

According to one aspect of the invention there is provided a quinazoline derivative of the Formula I



I

wherein m is 0, 1, 2 or 3;

each R¹ group, which may be the same or different, is selected from halogeno, trifluoromethyl, cyano, isocyano, nitro, hydroxy, mercapto, amino, formyl, carboxy, 5 carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphanyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, (3-6C)alkenoylamino, N-(1-6C)alkyl-10 (3-6C)alkenoylamino, (3-6C)alkynoylamino, N-(1-6C)alkyl-(3-6C)alkynoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :

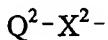
Q¹-X¹-

wherein X¹ is a direct bond or is selected from O, S, SO, SO₂, N(R⁴), CO, CH(OR⁴), 15 CON(R⁴), N(R⁴)CO, SO₂N(R⁴), N(R⁴)SO₂, OC(R⁴)₂, SC(R⁴)₂ and N(R⁴)C(R⁴)₂, wherein R⁴ is hydrogen or (1-6C)alkyl, and Q¹ is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl, or (R¹)_m is (1-3C)alkylenedioxy,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent 20 are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO₂, N(R⁵), CO, CH(OR⁵), CON(R⁵), N(R⁵)CO, SO₂N(R⁵), N(R⁵)SO₂, CH=CH and C≡C wherein R⁵ is hydrogen or (1-6C)alkyl or, when the inserted group is N(R⁵), R⁵ may also be (2-6C)alkanoyl,

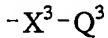
and wherein any CH₂=CH- or HC≡C- group within a R¹ substituent optionally bears at 25 the terminal CH₂= or HC≡ position a substituent selected from halogeno, carboxy, carbamoyl, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl,

amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl or from a group of the formula :



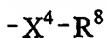
wherein X^2 is a direct bond or is selected from CO and $N(R^6)CO$, wherein R^6 is hydrogen or (1-6C)alkyl, and Q^2 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphanyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :

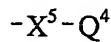


wherein X^3 is a direct bond or is selected from O, S, SO, SO_2 , $N(R^7)$, CO, $CH(OR^7)$, $CON(R^7)$, $N(R^7)CO$, $SO_2N(R^7)$, $N(R^7)SO_2$, $C(R^7)_2O$, $C(R^7)_2S$ and $N(R^7)C(R^7)_2$, wherein R^7 is hydrogen or (1-6C)alkyl, and Q^3 is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R^1 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphanyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



wherein X^4 is a direct bond or is selected from O and N(R^9), wherein R^9 is hydrogen or (1-6C)alkyl, and R^8 is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl or (1-6C)alkoxycarbonylamino-(1-6C)alkyl,
5 or from a group of the formula :



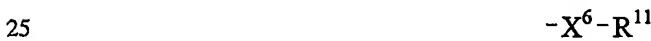
wherein X^5 is a direct bond or is selected from O, N(R^{10}) and CO, wherein R^{10} is hydrogen or (1-6C)alkyl, and Q^4 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same
10 or different, selected from halogeno, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl and (1-6C)alkoxy,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo or thioxo substituents;

R^2 is hydrogen or (1-6C)alkyl;

15 n is 0, 1, 2 or 3; and

R^3 is halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphanyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl,
20 N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, (3-6C)alkenylamino, N-(1-6C)alkyl-(3-6C)alkenylamino, (3-6C)alkenoylamino, (3-6C)alkynoylamino, N-(1-6C)alkyl-(3-6C)alkynoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



wherein X^6 is a direct bond or is selected from O and N(R^{12}), wherein R^{12} is hydrogen or (1-6C)alkyl, and R^{11} is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl or di-[(1-6C)alkyl]amino-(1-6C)alkyl, or from a group of the formula :



wherein X^7 is a direct bond or is selected from O, S, SO, SO₂, N(R^{13}), CO, CH(OR¹³), CON(R^{13}), N(R^{13})CO, SO₂N(R^{13}), N(R^{13})SO₂, C(R^{13})₂O, C(R^{13})₂S and N(R^{13})C(R^{13})₂,

wherein R¹³ is hydrogen or (1-6C)alkyl, and Q⁵ is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl and (1-6C)alkoxy, and any heterocyclyl group within Q⁵ 5 optionally bears 1 or 2 oxo or thioxo substituents, or a pharmaceutically-acceptable salt thereof.

In this specification the generic term "alkyl" includes both straight-chain and branched-chain alkyl groups such as propyl, isopropyl and tert-butyl, and also (3-7C)cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and 10 cycloheptyl. However references to individual alkyl groups such as "propyl" are specific for the straight-chain version only, references to individual branched-chain alkyl groups such as "isopropyl" are specific for the branched-chain version only and references to individual cycloalkyl groups such as "cyclopentyl" are specific for that 5-membered ring only. An analogous convention applies to other generic terms, for example (1-6C)alkoxy includes 15 methoxy, ethoxy, cyclopropoxy and cyclopentyloxy, (1-6C)alkylamino includes methylamino, ethylamino, cyclobutylamino and cyclohexylamino, and di-[(1-6Calkyl]amino includes dimethylamino, diethylamino, N-cyclobutyl-N-methylamino and N-cyclohexyl-N-ethylamino.

It is to be understood that, insofar as certain of the compounds of Formula I defined 20 above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses the above-mentioned activity. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic 25 form. Similarly, the above-mentioned activity may be evaluated using the standard laboratory techniques referred to hereinafter.

Suitable values for the generic radicals referred to above include those set out below.

A suitable value for any one of the 'Q' groups (Q¹ to Q⁵) when it is aryl or for the aryl group within a 'Q' group is, for example, phenyl or naphthyl, preferably phenyl.

30 A suitable value for any one of the 'Q' groups (Q¹ or Q³) when it is (3-7C)cycloalkyl or for the (3-7C)cycloalkyl group within a 'Q' group is, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or bicyclo[2.2.1]heptyl and a suitable value for any one of the 'Q' groups (Q¹ or Q³) when it is (3-7C)cycloalkenyl or for

the (3-7C)cycloalkenyl group within a 'Q' group is, for example, cyclobutenyl, cyclopentenyl, cyclohexenyl or cycloheptenyl.

A suitable value for any one of the 'Q' groups (Q¹ to Q⁵) when it is heteroaryl or for the heteroaryl group within a 'Q' group is, for example, an aromatic 5- or 6-membered 5 monocyclic ring or a 9- or 10-membered bicyclic ring with up to five ring heteroatoms selected from oxygen, nitrogen and sulphur, for example furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazenyl, benzofuranyl, indolyl, benzothienyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, indazolyl, benzofurazanyl, 10 quinolyl, isoquinolyl, quinazolinyl, quinoxalinyl, cinnolinyl or naphthyridinyl.

A suitable value for any one of the 'Q' groups (Q¹ to Q⁵) when it is heterocyclyl or for the heterocyclyl group within a 'Q' group is, for example, a non-aromatic saturated or partially saturated 3 to 10 membered monocyclic or bicyclic ring with up to five heteroatoms selected from oxygen, nitrogen and sulphur, for example oxiranyl, oxetanyl, tetrahydrofuranyl, 15 tetrahydropyranyl, oxepanyl, pyrrolinyl, pyrrolidinyl, morpholinyl, tetrahydro-1,4-thiazinyl, 1,1-dioxotetrahydro-1,4-thiazinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl, dihydropyridinyl, tetrahydropyridinyl, dihydropyrimidinyl or tetrahydropyrimidinyl, preferably tetrahydrofurananyl, tetrahydropyranyl, pyrrolidinyl, morpholinyl, 1,1-dioxotetrahydro-4H-1,4-thiazinyl, piperidinyl or piperazinyl. A suitable value for such a 20 group which bears 1 or 2 oxo or thioxo substituents is, for example, 2-oxopyrrolidinyl, 2-thioxopyrrolidinyl, 2-oxoimidazolidinyl, 2-thioxoimidazolidinyl, 2-oxopiperidinyl, 2,5-dioxopyrrolidinyl, 2,5-dioxoimidazolidinyl or 2,6-dioxopiperidinyl.

A suitable value for a 'Q' group when it is heteroaryl-(1-6C)alkyl is, for example, heteroarylmethyl, 2-heteroarylethyl and 3-heteroarylpropyl. The invention comprises 25 corresponding suitable values for 'Q' groups when, for example, rather than a heteroaryl-(1-6C)alkyl group, an aryl-(1-6C)alkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl-(1-6C)alkyl or heterocyclyl-(1-6C)alkyl group is present.

In structural Formula I there is a hydrogen atom at each of the 2- and 5-positions on the quinazoline ring. It is to be understood thereby that the R¹ substituents may only be 30 located at the 6-, 7- or 8-positions on the quinazoline ring i.e. that the 2- and 5-positions remain unsubstituted. It is further to be understood that the R³ group that may be present on the 2,3-methylenedioxyphenyl group within structural Formula I may be located on the phenyl ring or on the methylene group within the 2,3-methylenedioxy group. Preferably, any R³

group that is present on the 2,3-methylenedioxyphenyl group within structural Formula I is located on the phenyl ring thereof.

Suitable values for any of the 'R' groups (R^1 to R^{13}) or for various groups within an R^1 or R^3 substituent include:-

- | | |
|---|--|
| 5 for halogeno | fluoro, chloro, bromo and iodo; |
| for (1-6C)alkyl: | methyl, ethyl, propyl, isopropyl and <u>tert</u> -butyl; |
| for (2-8C)alkenyl: | vinyl, isopropenyl, allyl and but-2-enyl; |
| for (2-8C)alkynyl: | ethynyl, 2-propynyl and but-2-ynyl; |
| for (1-6C)alkoxy: | methoxy, ethoxy, propoxy, isopropoxy and butoxy; |
| 10 for (2-6C)alkenyloxy: | vinyloxy and allyloxy; |
| for (2-6C)alkynyoxy: | ethynyoxy and 2-propynyoxy; |
| for (1-6C)alkylthio: | methylthio, ethylthio and propylthio; |
| for (1-6C)alkylsulphinyl: | methylsulphinyl and ethylsulphinyl; |
| for (1-6C)alkylsulphonyl: | methylsulphonyl and ethylsulphonyl; |
| 15 for (1-6C)alkylamino: | methylamino, ethylamino, propylamino,
isopropylamino and butylamino; |
| for di-[(1-6C)alkyl]amino: | dimethylamino, diethylamino, <u>N</u> -ethyl-
<u>N</u> -methylamino and diisopropylamino; |
| 20 for <u>N</u> -(1-6C)alkylcarbamoyl: | <u>N</u> -methylcarbamoyl, <u>N</u> -ethylcarbamoyl and
<u>N</u> -propylcarbamoyl; |
| for <u>N,N</u> -di-[(1-6C)alkyl]carbamoyl: | <u>N,N</u> -dimethylcarbamoyl, <u>N</u> -ethyl-
<u>N</u> -methylcarbamoyl and <u>N,N</u> -diethylcarbamoyl; |
| 25 for (2-6C)alkanoyl: | acetyl and propionyl; |
| for (2-6C)alkanoyloxy: | acetoxyl and propionyloxy; |
| for (2-6C)alkanoylamino: | acetamido and propionamido; |
| for <u>N</u> -(1-6C)alkyl-(2-6C)alkanoylamino: | <u>N</u> -methylacetamido and <u>N</u> -methylpropionamido; |
| for <u>N</u> -(1-6C)alkylsulphamoyl: | <u>N</u> -methylsulphamoyl and <u>N</u> -ethylsulphamoyl; |
| 30 for <u>N,N</u> -di-[(1-6C)alkyl]sulphamoyl: | <u>N,N</u> -dimethylsulphamoyl; |
| for (1-6C)alkanesulphonylamino: | methanesulphonylamino and ethanesulphonylamino; |
| for <u>N</u> -(1-6C)alkyl-(1-6C)alkanesulphonylamino: | <u>N</u> -methylmethanesulphonylamino and
<u>N</u> -methylethanesulphonylamino; |

- for (3-6C)alkenoylamino: acrylamido, methacrylamido and crotonamido;
- for N-(1-6C)alkyl-(3-6C)alkenoylamino: N-methylacrylamido and N-methylcrotonamido;
- for (3-6C)alkynoylamino: propiolamido;
- for N-(1-6C)alkyl-(3-6C)alkynoylamino: N-methylpropiolamido;
- 5 for amino-(1-6C)alkyl: aminomethyl, 2-aminoethyl, 1-aminoethyl and 3-aminopropyl;
- for (1-6C)alkylamino-(1-6C)alkyl: methylaminomethyl, ethylaminomethyl, 1-methylaminooethyl, 2-methylaminooethyl, 2-ethylaminooethyl and 3-methylaminopropyl;
- 10 for di-[(1-6C)alkyl]amino-(1-6C)alkyl: dimethylaminomethyl, diethylaminomethyl, 1-dimethylaminoethyl, 2-dimethylaminoethyl and 3-dimethylaminopropyl;
- for halogeno-(1-6C)alkyl: chloromethyl, 2-chloroethyl, 1-chloroethyl and 3-chloropropyl;
- 15 for hydroxy-(1-6C)alkyl: hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl and 3-hydroxypropyl;
- for (1-6C)alkoxy-(1-6C)alkyl: methoxymethyl, ethoxymethyl, 1-methoxyethyl, 2-methoxyethyl, 2-ethoxyethyl and 3-methoxypropyl;
- 20 for cyano-(1-6C)alkyl: cyanomethyl, 2-cyanoethyl, 1-cyanoethyl and 3-cyanopropyl;
- for (2-6C)alkanoylamino-(1-6C)alkyl: acetamidomethyl, propionamidomethyl and 2-acetamidoethyl; and
- 25 for (1-6C)alkoxycarbonylamino-(1-6C)alkyl: methoxycarbonylaminomethyl, ethoxycarbonylaminomethyl, tert-butoxycarbonylaminomethyl and 2-methoxycarbonylaminooethyl.

A suitable value for $(R^1)_m$ when it is a (1-3C)alkylenedioxy group is, for example, methylenedioxy or ethylenedioxy and the oxygen atoms thereof occupy adjacent ring positions.

When, as defined hereinbefore, an R^1 group forms a group of the formula Q^1-X^1- and, for example, X^1 is a $OC(R^4)_2$ linking group, it is the carbon atom, not the oxygen atom, of the $OC(R^4)_2$ linking group which is attached to the quinazoline ring and the oxygen atom is

attached to the Q¹ group. Similarly, when, for example a CH₃ group within a R¹ substituent bears a group of the formula -X³-Q³ and, for example, X³ is a C(R⁷)₂O linking group, it is the carbon atom, not the oxygen atom, of the C(R⁷)₂O linking group which is attached to the CH₃ group and the oxygen atom is linked to the Q³ group. A similar convention applies to the attachment of the groups of the formulae Q²-X²- and -X⁷-Q⁵.

As defined hereinbefore, adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent may be optionally separated by the insertion into the chain of a group such as O, CON(R⁵) or C≡C. For example, insertion of a C≡C group into the ethylene chain within a 2-morpholinoethoxy group gives rise to a 4-morpholinobut-2-nyloxy group and, for example, insertion of a CONH group into the ethylene chain within a 3-methoxypropoxy group gives rise to, for example, a 2-(2-methoxyacetamido)ethoxy group.

When, as defined hereinbefore, any CH₂=CH- or HC≡C- group within a R¹ substituent optionally bears at the terminal CH₂= or HC≡ position a substituent such as a group of the formula Q²-X²- wherein X² is, for example, NHCO and Q² is a heterocyclyl-(1-6C)alkyl group, suitable R¹ substituents so formed include, for example, N-[heterocyclyl-(1-6C)alkyl]carbamoylvinyl groups such as N-(2-pyrrolidin-1-ylethyl)carbamoylvinyl or N-[heterocyclyl-(1-6C)alkyl]carbamylethynyl groups such as N-(2-pyrrolidin-1-ylethyl)carbamylethynyl.

When, as defined hereinbefore, any CH₂ or CH₃ group within a R¹ substituent optionally bears on each said CH₂ or CH₃ group one or more halogeno or (1-6C)alkyl substituents, there are suitably 1 or 2 halogeno or (1-6C)alkyl substituents present on each said CH₂ group and there are suitably 1, 2 or 3 such substituents present on each said CH₃ group.

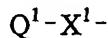
When, as defined hereinbefore, any CH₂ or CH₃ group within a R¹ substituent optionally bears on each said CH₂ or CH₃ group a substituent as defined hereinbefore, suitable R¹ substituents so formed include, for example, hydroxy-substituted heterocyclyl-(1-6C)alkoxy groups such as 2-hydroxy-3-piperidinopropoxy and 2-hydroxy-3-morpholinopropoxy, hydroxy-substituted amino-(2-6C)alkoxy groups such as 3-amino-2-hydroxypropoxy, hydroxy-substituted (1-6C)alkylamino-(2-6C)alkoxy groups such as 2-hydroxy-3-methylaminopropoxy, hydroxy-substituted di-[(1-6C)alkyl]amino-(2-6C)alkoxy groups such as 3-dimethylamino-2-hydroxypropoxy, hydroxy-substituted heterocyclyl-(1-6C)alkylamino groups such as 2-hydroxy-3-piperidinopropylamino and 2-hydroxy-3-morpholinopropylamino, hydroxy-substituted amino-(2-6C)alkylamino groups such as

3-amino-2-hydroxypropylamino, hydroxy-substituted (1-6C)alkylamino-(2-6C)alkylamino groups such as 2-hydroxy-3-methylaminopropylamino, hydroxy-substituted di-[(1-6C)alkyl]amino-(2-6C)alkylamino groups such as 3-dimethylamino-2-hydroxypropylamino, hydroxy-substituted (1-6C)alkoxy groups such as 2-hydroxyethoxy, 5 (1-6C)alkoxy-substituted (1-6C)alkoxy groups such as 2-methoxyethoxy and 3-ethoxypropoxy, (1-6C)alkylsulphonyl-substituted (1-6C)alkoxy groups such as 2-methylsulphonylethoxy and heterocyclyl-substituted (1-6C)alkylamino-(1-6C)alkyl groups such as 2-morpholinoethylaminomethyl, 2-piperazin-1-ylethylaminomethyl and 3-morpholinopropylaminomethyl.

10 A suitable pharmaceutically-acceptable salt of a compound of the Formula I is, for example, an acid-addition salt of a compound of the Formula I, for example an acid-addition salt with an inorganic or organic acid such as hydrochloric, hydrobromic, sulphuric, trifluoroacetic, citric or maleic acid; or, for example, a salt of a compound of the Formula I which is sufficiently acidic, for example an alkali or alkaline earth metal salt such as a 15 calcium or magnesium salt, or an ammonium salt, or a salt with an organic base such as methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

Particular novel compounds of the invention include, for example, quinazoline derivatives of the Formula I, or pharmaceutically-acceptable salts thereof, wherein, unless 20 otherwise stated, each of m, R¹, R², n and R³ has any of the meanings defined hereinbefore or in paragraphs (a) to (k) hereinafter :-

(a) m is 1 or 2, and each R¹ group, which may be the same or different, is selected from halogeno, trifluoromethyl, hydroxy, amino, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, 25 N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, (3-6C)alkenoylamino, N-(1-6C)alkyl-(3-6C)alkenoylamino, (3-6C)alkynoylamino and N-(1-6C)alkyl-(3-6C)alkynoylamino, or from a group of the formula :



30 wherein X¹ is a direct bond or is selected from O, N(R⁴), CON(R⁴), N(R⁴)CO and OC(R⁴)₂ wherein R⁴ is hydrogen or (1-6C)alkyl, and Q¹ is aryl, aryl-(1-6C)alkyl, cycloalkyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent are optionally separated by the insertion into the chain of a group selected from O, N(R⁵), CON(R⁵), N(R⁵)CO, CH=CH and C≡C wherein R⁵ is hydrogen or (1-6C)alkyl, or, when the inserted group is N(R⁵), R⁵ may also be (2-6C)alkanoyl,

- 5 and wherein any CH₂=CH- or HC≡C- group within a R¹ substituent optionally bears at the terminal CH₂= or HC≡ position a substituent selected from carbamoyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl or from a group of the formula :

10 Q^2-X^2-

wherein X² is a direct bond or is CO or N(R⁶)CO, wherein R⁶ is hydrogen or (1-6C)alkyl, and Q² is heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

- and wherein any CH₂ or CH₃ group within a R¹ substituent optionally bears on each said CH₂ or CH₃ group a substituent selected from hydroxy, amino, (1-6C)alkoxy, 15 (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (2-6C)alkanoyloxy, (2-6C)alkanoylamino and N-(1-6C)alkyl-(2-6C)alkanoylamino, or from a group of the formula :

$-X^3-Q^3$

- wherein X³ is a direct bond or is selected from O, N(R⁶), CON(R⁷), N(R⁷)CO and C(R⁷)₂O, 20 wherein R⁷ is hydrogen or (1-6C)alkyl, and Q³ is heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

- and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R¹ optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, hydroxy, amino, carbamoyl, (1-6C)alkyl, (1-6C)alkoxy, 25 N-(1-6C)alkylcarbamoyl and N,N-di-[(1-6C)alkyl]carbamoyl, or optionally bears 1 substituent selected from a group of the formula :

$-X^4-R^8$

- wherein X⁴ is a direct bond or is selected from O and N(R⁹), wherein R⁹ is hydrogen or (1-6C)alkyl, and R⁸ is hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, 30 amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl or (1-6C)alkoxycarbonylamino-(1-6C)alkyl, and from a group of the formula :

$-X^5-Q^4$

wherein X^5 is a direct bond or is selected from O, N(R^{10}) and CO, wherein R^{10} is hydrogen or (1-6C)alkyl, and Q^4 is heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl and 5 (1-6C)alkoxy,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo substituents;

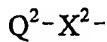
(b) m is 1 or 2, and each R^1 group, which may be the same or different, is selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl, propyl, butyl, vinyl, 10 ethynyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, methylamino, ethylamino, propylamino, dimethylamino, diethylamino, dipropylamino, N-methylcarbamoyl, N,N-dimethylcarbamoyl, acetamido, propionamido, acrylamido and propiolamido, or from a group of the formula :

Q^1-X^1-

15 wherein X^1 is a direct bond or is selected from O, NH, CONH, NHCO and OCH₂ and Q^1 is phenyl, benzyl, cyclopropylmethyl, 2-thienyl, 1-imidazolyl, 1,2,3-triazol-1-yl, 1,2,4-triazol-1-yl, 2-, 3- or 4-pyridyl, 2-imidazol-1-ylethyl, 3-imidazol-1-ylpropyl, 2-(1,2,3-triazolyl)ethyl, 3-(1,2,3-triazolyl)propyl, 2-(1,2,4-triazolyl)ethyl, 3-(1,2,4-triazolyl)propyl, 2-, 3- or 4-pyridylmethyl, 2-(2-, 3- or 4-pyridyl)ethyl, 20 3-(2-, 3- or 4-pyridyl)propyl, 1-, 2- or 3-pyrrolidinyl, morpholino, 1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl, piperidino, piperidin-3-yl, piperidin-4-yl, 1-, 3- or 4-homopiperidinyl, piperazin-1-yl, homopiperazin-1-yl, 1-, 2- or 3-pyrrolidinylmethyl, morpholinomethyl, piperidinomethyl, 3- or 4-piperidinylmethyl, 1-, 3- or 4-homopiperidinylmethyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-2-ylpropyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 25 3-pyrrolidin-1-ylpropyl, 4-pyrrolidin-1-ylbutyl, 2-morpholinoethyl, 3-morpholinopropyl, 4-morpholinobutyl, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethyl, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propyl, 2-piperidinoethyl, 3-piperidinopropyl, 4-piperidinobutyl, 2-piperidin-3-ylethyl, 3-piperidin-3-ylpropyl, 2-piperidin-4-ylethyl, 3-piperidin-4-ylpropyl, 2-homopiperidin-1-ylethyl, 3-homopiperidin-1-ylpropyl, 2-piperazin-1-ylethyl, 30 3-piperazin-1-ylpropyl, 4-piperazin-1-ylbutyl, 2-homopiperazin-1-ylethyl or 3-homopiperazin-1-ylpropyl,

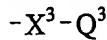
and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent are optionally separated by the insertion into the chain of a group selected from O, NH, CONH, NHCO, CH=CH and C≡C,

and wherein any CH₂=CH- or HC≡C- group within a R¹ substituent optionally bears at
 5 the terminal CH₂= or HC≡ position a substituent selected from carbamoyl,
N-methylcarbamoyl, N-ethylcarbamoyl, N-propylcarbamoyl, N,N-dimethylcarbamoyl,
 aminomethyl, 2-aminoethyl, 3-aminopropyl, 4-aminobutyl, methylaminomethyl,
 2-methylaminoethyl, 3-methylaminopropyl, 4-methylaminobutyl, dimethylaminomethyl,
 2-dimethylaminoethyl, 3-dimethylaminopropyl or 4-dimethylaminobutyl, or from a group of
 10 the formula :



wherein X² is a direct bond or is CO, NHCO or N(Me)CO and Q² is pyridyl, pyridylmethyl,
 2-pyridylethyl, pyrrolidin-1-yl, pyrrolidin-2-yl, morpholino, piperidino, piperidin-3-yl,
 piperidin-4-yl, piperazin-1-yl, pyrrolidin-1-ylmethyl, 2-pyrrolidin-1-yethyl,
 15 3-pyrrolidin-1-ylpropyl, 4-pyrrolidin-1-ylbutyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-yethyl,
 3-pyrrolidin-2-ylpropyl, morpholinomethyl, 2-morpholinoethyl, 3-morpholinopropyl,
 4-morpholinobutyl, piperidinomethyl, 2-piperidinoethyl, 3-piperidinopropyl,
 4-piperidinobutyl, piperidin-3-ylmethyl, 2-piperidin-3-yethyl, piperidin-4-ylmethyl,
 2-piperidin-4-yethyl, piperazin-1-ylmethyl, 2-piperazin-1-yethyl, 3-piperazin-1-ylpropyl or
 20 4-piperazin-1-ylbutyl,

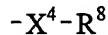
and wherein any CH₂ or CH₃ group within a R¹ substituent optionally bears on each
 said CH₂ or CH₃ group a substituent selected from hydroxy, amino, methoxy,
 methylsulphonyl, methylamino, dimethylamino, diisopropylamino, N-ethyl-N-methylamino,
N-isopropyl-N-methylamino, N-methyl-N-propylamino, acetoxy, acetamido and
 25 N-methylacetamido or from a group of the formula :



wherein X³ is a direct bond or is selected from O, NH, CONH, NHCO and CH₂O and Q³ is
 pyridyl, pyridylmethyl, pyrrolidin-1-yl, pyrrolidin-2-yl, morpholino, piperidino, piperidin-3-yl,
 piperidin-4-yl, piperazin-1-yl, 2-pyrrolidin-1-yethyl, 3-pyrrolidin-1-ylpropyl, pyrrolidin-
 30 2-ylmethyl, 2-pyrrolidin-2-yethyl, 3-pyrrolidin-2-ylpropyl, 2-morpholinoethyl,
 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, piperidin-3-ylmethyl, 2-piperidin-

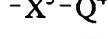
3-ylethyl, piperidin-4-ylmethyl, 2-piperidin-4-ylethyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl,

and wherein any aryl, heteroaryl or heterocycl group within a substituent on R¹ optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from 5 fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl, methoxy, N-methylcarbamoyl and N,N-dimethylcarbamoyl,
or optionally bears 1 substituent selected from a group of the formula :



wherein X⁴ is a direct bond or is selected from O and NH and R⁸ is 2-hydroxyethyl,

- 10 3-hydroxypropyl, 2-methoxyethyl, 3-methoxypropyl, cyanomethyl, aminomethyl, 2-aminoethyl, 3-aminopropyl, methylaminomethyl, 2-methylaminoethyl, 3-methylaminopropyl, 2-ethylaminoethyl, 3-ethylaminopropyl, dimethylaminomethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, acetamidomethyl, methoxycarbonylaminomethyl, ethoxycarbonylaminomethyl or
- 15 tert-butoxycarbonylaminomethyl, and from a group of the formula :



wherein X⁵ is a direct bond or is selected from O, NH and CO and Q⁴ is

pyrrolidin-1-ylmethyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, morpholinomethyl, 2-morpholinoethyl, 3-morpholinopropyl, piperidinomethyl, 2-piperidinoethyl, 20 3-piperidinopropyl, piperazin-1-ylmethyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl, each of which optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, methyl and methoxy,

and wherein any heterocycl group within a substituent on R¹ optionally bears 1 or 2 oxo substituents;

- 25 (c) m is 1 or 2 and each R¹ group, which may be the same or different, is located at the 6- and/or 7-positions and is selected from hydroxy, amino, methyl, ethyl, propyl, butyl, vinyl, ethynyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, methylamino, ethylamino, dimethylamino, diethylamino, acetamido, propionamido, cyclopentyloxy, cyclohexyloxy, phenoxy, benzyloxy, tetrahydrofuran-3-yloxy, tetrahydropyran-3-yloxy, 30 tetrahydropyran-4-yloxy, cyclopropylmethoxy, 2-imidazol-1-ylethoxy, 3-imidazol-1-ylpropoxy, 2-(1,2,3-triazol-1-yl)ethoxy, 3-(1,2,3-triazol-1-yl)propoxy, 2-(1,2,4-triazol-1-yl)ethoxy, 3-(1,2,4-triazol-1-yl)propoxy, pyrid-2-ylmethoxy, pyrid-3-ylmethoxy, pyrid-4-ylmethoxy, 2-pyrid-2-ylethoxy,

- 2-pyrid-3-yloxy, 2-pyrid-4-yloxy, 3-pyrid-2-ylpropoxy, 3-pyrid-3-ylpropoxy,
 3-pyrid-4-ylpropoxy, pyrrolidin-1-yl, morpholino, piperidino, piperazin-1-yl,
 2-pyrrolidin-1-yloxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy,
 pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-yloxy,
- 5 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy,
 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-
 yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, piperidin-3-yloxy,
 piperidin-4-yloxy, piperidin-3-ylmethoxy, piperidin-4-ylmethoxy, 2-piperidin-3-yloxy,
 3-piperidin-3-ylpropoxy, 2-piperidin-4-yloxy, 3-piperidin-4-ylpropoxy,
- 10 2-homopiperidin-1-yloxy, 3-homopiperidin-1-ylpropoxy, 2-piperazin-1-yloxy,
 3-piperazin-1-ylpropoxy, 4-piperazin-1-ylbutoxy, 2-homopiperazin-1-yloxy,
 3-homopiperazin-1-ylpropoxy, 2-pyrrolidin-1-yethylamino, 3-pyrrolidin-1-ylpropylamino,
 4-pyrrolidin-1-ylbutylamino, pyrrolidin-3-ylamino, pyrrolidin-2-ylmethylamino, 2-pyrrolidin-
 2-yethylamino, 3-pyrrolidin-2-ylpropylamino, 2-morpholinoethylamino,
- 15 3-morpholinopropylamino, 4-morpholinobutylamino, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-
 4-yl)ethylamino, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propylamino,
 2-piperidinoethylamino, 3-piperidinopropylamino, 4-piperidinobutylamino,
 piperidin-3-ylamino, piperidin-4-ylamino, piperidin-3-ylmethylamino,
 2-piperidin-3-yethylamino, piperidin-4-ylmethylamino, 2-piperidin-4-yethylamino,
- 20 2-homopiperidin-1-yethylamino, 3-homopiperidin-1-ylpropylamino,
 2-piperazin-1-yethylamino, 3-piperazin-1-ylpropylamino, 4-piperazin-1-ylbutylamino,
 2-homopiperazin-1-yethylamino or 3-homopiperazin-1-ylpropylamino,
 and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent
 are optionally separated by the insertion into the chain of a group selected from O, NH,
- 25 CH=CH and C≡C,
 and when R¹ is a vinyl or ethynyl group, the R¹ substituent optionally bears at the
 terminal CH₂= or HC≡ position a substituent selected from
N-(2-dimethylaminoethyl)carbamoyl, N-(3-dimethylaminopropyl)carbamoyl,
 methylaminomethyl, 2-methylaminoethyl, 3-methylaminopropyl, 4-methylaminobutyl,
- 30 dimethylaminomethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl and
 4-dimethylaminobutyl, or from a group of the formula :

Q²-X²-

wherein X² is a direct bond or is NHCO or N(Me)CO and Q² is imidazolylmethyl, 2-imidazolylethyl, 3-imidazolylpropyl, pyridylmethyl, 2-pyridylethyl, 3-pyridylpropyl, pyrrolidin-1-ylmethyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, 4-pyrrolidin-1-ylbutyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-2-ylpropyl, morpholinomethyl,

5 2-morpholinoethyl, 3-morpholinopropyl, 4-morpholinobutyl, piperidinomethyl, 2-piperidinoethyl, 3-piperidinopropyl, 4-piperidinobutyl, piperidin-3-ylmethyl, 2-piperidin-3-ylethyl, piperidin-4-ylmethyl, 2-piperidin-4-ylethyl, piperazin-1-ylmethyl, 2-piperazin-1-ylethyl, 3-piperazin-1-ylpropyl or 4-piperazin-1-ylbutyl,

and wherein any CH₂ or CH₃ group within a R¹ substituent optionally bears on each
10 said CH₂ or CH₃ group a substituent selected from hydroxy, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino, N-ethyl-N-methylamino, N-isopropyl-N-methylamino, N-methyl-N-propylamino, acetoxy, acetamido and N-methylacetamido,

and wherein any phenyl, imidazolyl, triazolyl, pyridyl or heterocyclyl group within a
15 substituent on R¹ optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl, N-methylcarbamoyl, N,N-dimethylcarbamoyl and methoxy, and a pyrrolidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl or homopiperazin-1-yl group within a R¹ substituent is optionally N-substituted with 2-methoxyethyl, 3-methoxypipropyl, cyanomethyl,
20 2-aminoethyl, 3-aminopropyl, 2-methylaminoethyl, 3-methylaminopropyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl, the last 8 of which substituents each optionally bears 1 or 2 substituents, which may be the same or different,
25 selected from fluoro, chloro, methyl and methoxy,

and wherein any heterocyclyl group within a substituent on R¹ optionally bears 1 or 2 oxo substituents;

(d) m is 1 and the R¹ group is located at the 6- or 7-position and is selected from hydroxy, amino, methyl, ethyl, propyl, butyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, 30 methylamino, ethylamino, dimethylamino, diethylamino, acetamido, propionamido, benzyloxy, 2-imidazol-1-ylethoxy, 2-(1,2,3-triazol-1-yl)ethoxy, 2-(1,2,4-triazol-1-yl)ethoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy,

3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy,
2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-
4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy,
piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, 2-piperidin-3-ylethoxy,
5 piperidin-4-ylmethoxy, 2-piperidin-4-ylethoxy, 2-homopiperidin-1-ylethoxy,
3-homopiperidin-1-ylpropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy,
2-homopiperazin-1-ylethoxy or 3-homopiperazin-1-ylpropoxy,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent
are optionally separated by the insertion into the chain of a group selected from O, NH,

10 CH=CH and C≡C,

and wherein any CH₂ or CH₃ group within a R¹ substituent optionally bears on each
said CH₂ or CH₃ group a substituent selected from hydroxy, amino, methoxy,
methylsulphonyl, methylamino, dimethylamino, diisopropylamino, N-ethyl-N-methylamino,
N-isopropyl-N-methylamino and acetoxy,

15 and wherein any phenyl or heterocyclyl group within a substituent on R¹ optionally
bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro,
trifluoromethyl, hydroxy, amino, methyl, ethyl and methoxy,

and wherein any heterocyclyl group within a substituent on R¹ optionally bears 1 or 2
oxo substituents;

20 (e) R² is hydrogen;

(f) n is 1 or 2 and the R³ groups, which may be the same or different, are located at the
5- and/or 6-positions of the 2,3-methylenedioxyphenyl group and are selected from halogeno,
trifluoromethyl, cyano, hydroxy, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl and (1-6C)alkoxy;

(g) n is 1 or 2 and the R³ groups, which may be the same or different, are located at the
25 5- and/or 6-positions of the 2,3-methylenedioxyphenyl group and are selected from fluoro,
chloro, bromo, iodo, trifluoromethyl, cyano, hydroxy, methyl, ethyl, vinyl, allyl, isopropenyl,
ethynyl, 1-propynyl, 2-propynyl, methoxy and ethoxy;

(h) n is 1 and the R³ group is located at the 5- or 6-position of the
2,3-methylenedioxyphenyl group, especially the 6-position, and is selected from chloro,
30 bromo, trifluoromethyl, cyano, hydroxy, methyl, ethyl, methoxy and ethoxy;

(i) n is 1 and the R³ group is located at the 6-position of the 2,3-methylenedioxyphenyl
group and is selected from chloro, bromo and trifluoromethyl;

- (j) n is 0; and
- (k) m is 2 and each R¹ group, which may be the same or different, is located at the 6- and/or 7-positions and is selected from hydroxy, amino, methyl, ethyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, methylamino, ethylamino, dimethylamino, diethylamino,
- 5 acetamido, propionamido, benzyloxy, 2-pyrrol-1-yethoxy, 3-pyrrol-1-ylpropoxy, 2-imidazol-1-yethoxy, 3-imidazol-1-ylpropoxy, 2-(1,2,3-triazol-1-yl)ethoxy, 3-(1,2,3-triazol-1-yl)propoxy, 2-(1,2,4-triazol-1-yl)ethoxy, 3-(1,2,4-triazol-1-yl)propoxy, 2-pyridylmethoxy, 3-pyridylmethoxy, 4-pyridylmethoxy, 2-tetrahydropyran-4-yethoxy, 3-tetrahydropyran-4-ylpropoxy, 2-pyrrolidin-1-yethoxy, 3-pyrrolidin-1-ylpropoxy,
- 10 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-yethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, piperidin-4-ylmethoxy,
- 15 2-piperidin-3-yethoxy, 3-piperidin-3-ylpropoxy, 2-piperidin-4-yethoxy, 3-piperidin-4-ylpropoxy, 2-homopiperidin-1-yethoxy, 3-homopiperidin-1-ylpropoxy, 2-piperazin-1-yethoxy, 3-piperazin-1-ylpropoxy, 4-piperazin-1-ylbutoxy, 2-homopiperazin-1-yethoxy or 3-homopiperazin-1-ylpropoxy,
- and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent
- 20 are optionally separated by the insertion into the chain of a group selected from O, NH, CH=CH and C≡C,
- and wherein any CH₂ or CH₃ group within a R¹ substituent optionally bears on each said CH₂ or CH₃ group a substituent selected from hydroxy, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diethylamino, diisopropylamino,
- 25 N-ethyl-N-methylamino, N-isopropyl-N-methylamino, N-isobutyl-N-methylamino, N-allyl-N-methylamino, acetoxy, acetamido, N-methylacetamido, 2-pyridyloxy, 3-pyridyloxy and 4-pyridyloxy,
- and wherein any phenyl, pyrrolyl, imidazolyl, triazolyl, pyridyl or heterocyclyl group within a substituent on R¹ optionally bears 1, 2 or 3 substituents, which may be the same or
- 30 different, selected from fluoro, chloro, trifluoromethyl, cyano, hydroxy, amino, carbamoyl, methyl, ethyl, N-methylcarbamoyl, N,N-dimethylcarbamoyl, methoxy, methoxymethyl and morpholinomethyl, and a pyrrolidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl or

homopiperazin-1-yl group within a R¹ substituent is optionally N-substituted with methyl, ethyl, 2-methoxyethyl, 3-methoxypropyl, cyanomethyl, 2-aminoethyl, 3-aminopropyl, 2-methylaminoethyl, 3-methylaminopropyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, 2-pyrrolidin-1-yethyl, 3-pyrrolidin-1-ylpropyl, 2-morpholinoethyl, 3-morpholinopropyl, 5 2-piperidinoethyl, 3-piperidinopropyl, 2-piperazin-1-yethyl or 3-piperazin-1-ylpropyl, the last 8 of which substituents each optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, methyl and methoxy,
and wherein any heterocyclyl group within a substituent on R¹ optionally bears 1 or 2 oxo substituents.

10 A preferred compound of the invention is a quinazoline derivative of the Formula I
wherein :

m is 1 or 2 and each R¹ group, which may be the same or different, is located at the 6- and/or 7-positions and is selected from hydroxy, amino, methyl, ethyl, propyl, butyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, methylamino, ethylamino, dimethylamino, 15 diethylamino, acetamido, propionamido, 2-imidazol-1-yethoxy, 2-(1,2,4-triazol-1-yl)ethoxy, 2-pyrrolidin-1-yethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-yethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin- 20 4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, piperidin-4-ylmethoxy, 2-piperidin-3-yethoxy, 3-piperidin-3-ylpropoxy, 2-piperidin-4-yethoxy, 3-piperidin-4-ylpropoxy, 2-homopiperidin-1-yethoxy, 3-homopiperidin-1-ylpropoxy, 25 2-piperazin-1-yethoxy, 3-piperazin-1-ylpropoxy, 4-piperazin-1-ylbutoxy, 2-homopiperazin-1-yethoxy and 3-homopiperazin-1-ylpropoxy,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent are optionally separated by the insertion into the chain of a group selected from O, NH, CH=CH and C≡C,

and wherein any CH₂ or CH₃ group within a R¹ substituent optionally bears on each 30 said CH₂ or CH₃ group a substituent selected from hydroxy, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diethylamino, N-ethyl-N-methylamino, N-isopropyl-N-methylamino, N-methyl-N-propylamino and acetoxy;

and wherein any heteroaryl or heterocycl group within a substituent on R¹ optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl, methoxy, N-methylcarbamoyl and N,N-dimethylcarbamoyl and a pyrrolidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl or 5 homopiperazin-1-yl group within a R¹ substituent is optionally N-substituted with 2-methoxyethyl, 3-methoxypropyl, cyanomethyl, 2-aminoethyl, 3-aminopropyl, 2-methylaminoethyl, 3-methylaminopropyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-piperazin-1-ylethyl or 10 3-piperazin-1-ylpropyl, the last 8 of which substituents each optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, methyl and methoxy,

and wherein any heterocycl group within a substituent on R¹ optionally bears 1 or 2 oxo substituents;

15 R² is hydrogen;

n is 0 or 1 and the R³ group, if present, is located at the 5- or 6-position of the 2,3-methylenedioxyphenyl group and is selected from fluoro, chloro, trifluoromethyl, cyano, hydroxy, methyl, ethyl, vinyl, allyl, ethynyl, methoxy and ethoxy; or a pharmaceutically-acceptable acid-addition salt thereof.

20 A further preferred compound of the invention is a quinazoline derivative of the Formula I wherein :

m is 2 and each R¹ group, which may be the same or different, is located at the 6- and/or 7-positions and is selected from hydroxy, amino, methyl, ethyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, methylamino, ethylamino, dimethylamino, diethylamino, 25 acetamido, propionamido, benzyloxy, 2-pyrrol-1-ylethoxy, 3-pyrrol-1-ylpropoxy, 2-imidazol-1-ylethoxy, 3-imidazol-1-ylpropoxy, 2-(1,2,3-triazol-1-yl)ethoxy, 3-(1,2,3-triazol-1-yl)propoxy, 2-pyridylmethoxy, 3-pyridylmethoxy, 4-pyridylmethoxy, 2-tetrahydropyran-4-ylethoxy, 3-tetrahydropyran-4-ylpropoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 30 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy,

piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, piperidin-4-ylmethoxy,
2-piperidin-3-yethoxy, 3-piperidin-3-ylpropoxy, 2-piperidin-4-yethoxy,
3-piperidin-4-ylpropoxy, 2-homopiperidin-1-yethoxy, 3-homopiperidin-1-ylpropoxy,
2-piperazin-1-yethoxy, 3-piperazin-1-ylpropoxy, 4-piperazin-1-ylbutoxy,
5 2-homopiperazin-1-yethoxy or 3-homopiperazin-1-ylpropoxy,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent
are optionally separated by the insertion into the chain of a group selected from O, NH,
CH=CH and C≡C,

and wherein any CH₂ or CH₃ group within a R¹ substituent optionally bears on each
10 said CH₂ or CH₃ group a substituent selected from hydroxy, amino, methoxy,
methylsulphonyl, methylamino, dimethylamino, diethylamino, diisopropylamino,
N-ethyl-N-methylamino, N-isopropyl-N-methylamino, N-isobutyl-N-methylamino,
N-allyl-N-methylamino, acetoxy, acetamido, N-methylacetamido, 2-pyridyloxy, 3-pyridyloxy
and 4-pyridyloxy,

15 and wherein any phenyl, pyrrolyl, imidazolyl, triazolyl, pyridyl or heterocyclyl group
within a substituent on R¹ optionally bears 1, 2 or 3 substituents, which may be the same or
different, selected from fluoro, chloro, trifluoromethyl, cyano, hydroxy, amino, carbamoyl,
methyl, ethyl, N-methylcarbamoyl, N,N-dimethylcarbamoyl, methoxy, methoxymethyl and
morpholinomethyl, and a pyrrolidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl or
20 homopiperazin-1-yl group within a R¹ substituent is optionally N-substituted with methyl,
ethyl, 2-methoxyethyl, 3-methoxypropyl, cyanomethyl, 2-aminoethyl, 3-aminopropyl,
2-methylaminoethyl, 3-methylaminopropyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl,
2-pyrrolidin-1-yethyl, 3-pyrrolidin-1-ylpropyl, 2-morpholinoethyl, 3-morpholinopropyl,
2-piperidinoethyl, 3-piperidinopropyl, 2-piperazin-1-yethyl or 3-piperazin-1-ylpropyl,
25 the last 8 of which substituents each optionally bears 1 or 2 substituents, which may be the
same or different, selected from fluoro, chloro, methyl and methoxy,

and wherein any heterocyclyl group within a substituent on R¹ optionally bears 1 or 2
oxo substituents;

R² is hydrogen;

30 n is 0 or 1 and the R³ group, if present, is located at the 6-position of the
2,3-methylenedioxyphenyl group and is selected from chloro, bromo and trifluoromethyl;
or a pharmaceutically-acceptable acid-addition salt thereof.

A further preferred compound of the invention is a quinazoline derivative of the Formula I wherein :

- m is 2 and the first R¹ group is located at the 6-position and is selected from hydroxy, 5 methoxy, ethoxy and propoxy, and the second R¹ group is located at the 7-position and is selected from 2-dimethylaminoethoxy, 3-dimethylaminopropoxy, 4-dimethylaminobutoxy, 2-diethylaminoethoxy, 3-diethylaminopropoxy, 4-diethylaminobutoxy, 2-diisopropylaminoethoxy, 3-diisopropylaminopropoxy, 4-diisopropylaminobutoxy, 2-(N-isopropyl-N-methylamino)ethoxy, 3-(N-isopropyl-N-methylamino)propoxy, 10 4-(N-isopropyl-N-methylamino)butoxy, 2-pyrrolidin-1-yethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy, N-methylpyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-yethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-15 4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, piperidin-3-yloxy, N-methylpiperidin-3-yloxy, piperidin-4-yloxy, N-methylpiperidin-4-yloxy, piperidin-3-ylmethoxy, N-methylpiperidin-3-ylmethoxy, piperidin-4-ylmethoxy, N-methylpiperidin-4-ylmethoxy, 2-piperidin-3-yethoxy, 2-(N-methylpiperidin-3-yl)ethoxy, 3-piperidin-3-ylpropoxy, 3-(N-methylpiperidin-3-yl)propoxy, 2-piperidin-4-yethoxy, 20 2-(N-methylpiperidin-4-yl)ethoxy, 3-piperidin-4-ylpropoxy, 3-(N-methylpiperidin-4-yl)propoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 4-(4-methylpiperazin-1-yl)butoxy, 2-(4-cyanomethylpiperazin-1-yl)ethoxy, 3-(4-cyanomethylpiperazin-1-yl)propoxy, 4-(4-cyanomethylpiperazin-1-yl)butoxy, 2-[2-(4-methylpiperazin-1-yl)ethoxy]ethoxy, 25 2-methylsulphonylethoxy and 3-methylsulphonylpropoxy,
- and wherein any CH₂ group within the second R¹ group that is attached to two carbon atoms optionally bears a hydroxy group or acetoxy group on said CH₂ group,
- and wherein any heterocyclyl group within the second R¹ group optionally bears 1 or 2 oxo substituents;
- 30 R² is hydrogen; and
- n is 0 or n is 1 and the R³ group is located at the 5- or 6-position of the 2,3-methylenedioxyphenyl group and is selected from fluoro, chloro, trifluoromethyl, cyano, methyl, ethyl, ethynyl, methoxy and ethoxy;

or a pharmaceutically-acceptable acid-addition salt thereof.

A further preferred compound of the invention is a quinazoline derivative of the Formula I wherein :

- m is 2 and the first R¹ group is a 6-methoxy group and the second R¹ group is located
5 at the 7-position and is selected from 2-dimethylaminoethoxy, 3-dimethylaminopropoxy,
4-dimethylaminobutoxy, 2-diethylaminoethoxy, 3-diethylaminopropoxy,
4-diethylaminobutoxy, 2-diisopropylaminoethoxy, 3-diisopropylaminopropoxy,
4-diisopropylaminobutoxy, 2-(N-isopropyl-N-methylamino)ethoxy,
3-(N-isopropyl-N-methylamino)propoxy, 4-(N-isopropyl-N-methylamino)butoxy,
10 2-(N-isobutyl-N-methylamino)ethoxy, 3-(N-isobutyl-N-methylamino)propoxy,
4-(N-isobutyl-N-methylamino)butoxy, 2-(N-allyl-N-methylamino)ethoxy,
3-(N-allyl-N-methylamino)propoxy, 4-(N-allyl-N-methylamino)butoxy,
2-pyrrolidin-1-yloxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy,
pyrrolidin-3-yloxy, N-methylpyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy,
15 2-pyrrolidin-2-yloxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy,
3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-
4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy,
3-piperidinopropoxy, 4-piperidinobutoxy, piperidin-3-yloxy, N-methylpiperidin-3-yloxy,
piperidin-4-yloxy, N-methylpiperidin-4-yloxy, piperidin-3-ylmethoxy,
20 N-methylpiperidin-3-ylmethoxy, N-cyanomethylpiperidin-3-ylmethoxy,
piperidin-4-ylmethoxy, N-methylpiperidin-4-ylmethoxy, N-cyanomethylpiperidin-
4-ylmethoxy, 2-piperidin-3-yloxy, 2-(N-methylpiperidin-3-yl)ethoxy,
3-piperidin-3-ylpropoxy, 3-(N-methylpiperidin-3-yl)propoxy, 2-piperidin-4-yloxy,
2-(N-methylpiperidin-4-yl)ethoxy, 3-piperidin-4-ylpropoxy, 3-(N-methylpiperidin-
25 4-yl)propoxy, 2-homopiperidin-1-yloxy, 3-homopiperidin-1-ylpropoxy,
4-homopiperidin-1-ylbutoxy, 2-piperazin-1-yloxy, 2-(4-methylpiperazin-1-yl)ethoxy,
3-piperazin-1-ylpropoxy, 3-(4-methylpiperazin-1-yl)propoxy, 4-piperazin-1-ylbutoxy,
4-(4-methylpiperazin-1-yl)butoxy, 2-(4-cyanomethylpiperazin-1-yl)ethoxy,
3-(4-cyanomethylpiperazin-1-yl)propoxy, 4-(4-cyanomethylpiperazin-1-yl)butoxy,
30 2-(2-piperazin-1-yloxy)ethoxy, 2-[2-(4-methylpiperazin-1-yl)ethoxy]ethoxy,
2-methylsulphonylethoxy, 3-methylsulphonylpropoxy, 2-tetrahydropyran-4-yloxy,
3-tetrahydropyran-4-ylpropoxy, 2-pyrrol-1-yloxy, 3-pyrrol-1-ylpropoxy,
2-(2-pyridyloxy)ethoxy, 3-(2-pyridyloxy)propoxy, 2-(3-pyridyloxy)ethoxy,

- 3-(3-pyridyloxy)propoxy, 2-(4-pyridyloxy)ethoxy, 3-(4-pyridyloxy)propoxy,
2-pyridylmethoxy, 3-pyridylmethoxy and 4-pyridylmethoxy,
and wherein any CH₂ group within the second R¹ group that is attached to two carbon
atoms optionally bears a hydroxy group on said CH₂ group,
- 5 and wherein any heteroaryl group within the second R¹ group optionally bears 1 or 2
substituents selected from chloro, cyano, hydroxy and methyl, and any heterocyclyl group
within the second R¹ group optionally bears 1 or 2 substituents selected from hydroxy, methyl
and oxo;
- R² is hydrogen; and
- 10 n is 0 or n is 1 and the R³ group is located at the 6-position of the
2,3-methylenedioxyphenyl group and is selected from chloro and bromo;
or a pharmaceutically-acceptable acid-addition salt thereof.
- A further preferred compound of the invention is a quinazoline derivative of the
Formula I wherein :
- 15 m is 2 and the first R¹ group is a 6-methoxy group and the second R¹ group is located
at the 7-position and is selected from 2-pyrrolidin-1-yethoxy, 3-pyrrolidin-1-ylpropoxy,
2-morpholinoethoxy, 3-morpholinopropoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-
4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy,
3-piperidinopropoxy, piperidin-3-ylmethoxy, N-methylpiperidin-3-ylmethoxy,
20 piperidin-4-ylmethoxy, N-methylpiperidin-4-ylmethoxy, 2-piperidin-3-yethoxy,
2-(N-methylpiperidin-3-yl)ethoxy, 3-piperidin-3-ylpropoxy, 3-(N-methylpiperidin-
3-yl)propoxy, 2-piperidin-4-yethoxy, 2-(N-methylpiperidin-4-yl)ethoxy,
3-piperidin-4-ylpropoxy, 3-(N-methylpiperidin-4-yl)propoxy,
2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy,
25 2-(4-cyanomethylpiperazin-1-yl)ethoxy, 3-(4-cyanomethylpiperazin-1-yl)propoxy,
2-[2-(4-methylpiperazin-1-yl)ethoxy]ethoxy, 2-methylsulphonylethoxy,
3-methylsulphonylpropoxy, 2-(4-pyridyloxy)ethoxy, 3-pyridylmethoxy and
2-cyanopyrid-4-ylmethoxy;
- R² is hydrogen; and
- 30 n is 0 or n is 1 and the R³ group is located at the 6-position of the
2,3-methylenedioxyphenyl group and is selected from chloro and bromo;
or a pharmaceutically-acceptable acid-addition salt thereof.

A further preferred compound of the invention is a quinazoline derivative of the Formula I wherein :

m is 2 and the first R¹ group is a 6-methoxy group and the second R¹ group is located at the 7-position and is selected from 3-(N-isopropyl-N-methylamino)propoxy,
5 3-pyrrolidin-1-ylpropoxy, 3-morpholinopropoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 3-piperidinopropoxy, N-methylpiperidin-4-ylmethoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 3-(4-cyanomethylpiperazin-1-yl)propoxy and 2-[2-(4-methylpiperazin-1-yl)ethoxy]ethoxy,
and wherein any CH₂ group within the second R¹ group that is attached to two carbon
10 atoms optionally bears a hydroxy group on said CH₂ group;

R² is hydrogen; and

n is 0;

or a pharmaceutically-acceptable acid-addition salt thereof.

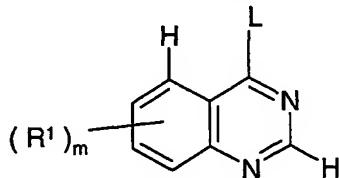
A particular preferred compound of the invention is, for example, a quinazoline derivative of the Formula I selected from:-
15 6-methoxy-4-(2,3-methylenedioxyanilino)-7-(3-morpholinopropoxy)quinazoline,
6-methoxy-4-(2,3-methylenedioxyanilino)-7-[3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy]quinazoline,
6-methoxy-4-(2,3-methylenedioxyanilino)-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,
20 6-methoxy-4-(2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]quinazoline,
6-methoxy-4-(2,3-methylenedioxyanilino)-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline,
6-methoxy-4-(2,3-methylenedioxyanilino)-7-(3-piperidinopropoxy)quinazoline,
6-methoxy-4-(2,3-methylenedioxyanilino)-7-(N-methylpiperidin-4-ylmethoxy)quinazoline,
25 7-(2-hydroxy-3-pyrrolidin-1-ylpropoxy)-6-methoxy-4-(2,3-methylenedioxyanilino)-
7-[2-hydroxy-3-(N-isopropyl-N-methylamino)propoxy]-6-methoxy-
4-(2,3-methylenedioxyanilino)quinazoline,
7-[3-(4-cyanomethylpiperazin-1-yl)-2-hydroxypropoxy]-6-methoxy-
4-(2,3-methylenedioxyanilino)quinazoline and
30 6-methoxy-4-(2,3-methylenedioxyanilino)-7-{2-[2-(4-methylpiperazin-1-yl)ethoxy]ethoxy}quinazoline;
or a pharmaceutically-acceptable acid-addition salt thereof.

A further particular preferred compound of the invention is, for example, a quinazoline derivative of the Formula I selected from:-

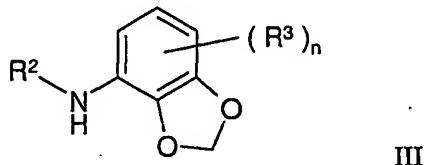
- 4-(6-chloro-2,3-methylenedioxyanilino)-7-[3-(4-cyanomethylpiperazin-1-yl)propoxy]-6-methoxyquinazoline,
- 5 4-(6-chloro-2,3-methylenedioxyanilino)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,
- 4-(6-chloro-2,3-methylenedioxyanilino)-6-methoxy-7-(3-piperidinopropoxy)quinazoline,
- 4-(6-bromo-2,3-methylenedioxyanilino)-6-methoxy-7-(3-piperidinopropoxy)quinazoline,
- 6-methoxy-4-(2,3-methylenedioxyanilino)-7-[2-(N-methylpiperidin-4-yl)ethoxy]quinazoline,
- 6-methoxy-4-(2,3-methylenedioxyanilino)-7-[2-(4-pyridyloxy)ethoxy]quinazoline,
- 10 6-methoxy-4-(2,3-methylenedioxyanilino)-7-(3-pyridylmethoxy)quinazoline,
- 4-(6-chloro-2,3-methylenedioxyanilino)-7-(2-cyanopyrid-4-ylmethoxy)-6-methoxyquinazoline and
- 4-(6-chloro-2,3-methylenedioxyanilino)-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline;
- 15 or a pharmaceutically-acceptable acid-addition salt thereof.

A quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Such processes, when used to prepare a quinazoline derivative of the Formula I are provided as a further feature of the invention and are illustrated 20 by the following representative process variants in which, unless otherwise stated, m, R¹, R², n and R³ have any of the meanings defined hereinbefore. Necessary starting materials may be obtained by standard procedures of organic chemistry. The preparation of such starting materials is described in conjunction with the following representative process variants and within the accompanying Examples. Alternatively necessary starting materials are obtainable 25 by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist.

(a) The reaction of a quinazoline of the Formula II



wherein L is a displaceable group and m and R¹ have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with an aniline of the Formula III



5 wherein R², n and R³ have any of the meanings defined hereinbefore except that any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means.

The reaction may conveniently be carried out in the presence of a suitable acid or in the presence of a suitable base. A suitable acid is, for example, an inorganic acid such as, for 10 example, hydrogen chloride or hydrogen bromide. A suitable base is, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine, N-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene, or, for example, an alkali or alkaline earth metal carbonate or hydroxide, for example sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium 15 hydroxide, or, for example, an alkali metal hydride, for example sodium hydride.

A suitable displaceable group L is, for example, a halogeno, alkoxy, aryloxy or sulphonyloxy group, for example a chloro, bromo, methoxy, phenoxy, pentafluorophenoxy, methanesulphonyloxy or toluene-4-sulphonyloxy group. The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent, for example an alcohol or ester such 20 as methanol, ethanol, isopropanol or ethyl acetate, a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride, an ether such as tetrahydrofuran or 1,4-dioxan, an aromatic solvent such as toluene, or a dipolar aprotic solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethylsulphoxide. The reaction is conveniently carried out at a temperature in the range, 25 for example, 10 to 250°C, preferably in the range 40 to 120°C.

Typically, the quinazoline of the Formula II may be reacted with an aniline of the Formula III in the presence of a protic solvent such as isopropanol, conveniently in the presence of an acid, for example hydrogen chloride gas in diethyl ether, and at a temperature in the range, for example, 25 to 150°C, preferably at or near the reflux temperature of the 30 reaction solvent.

The quinazoline derivative of the Formula I may be obtained from this process in the form of the free base or alternatively it may be obtained in the form of a salt with the acid of the formula H-L wherein L has the meaning defined hereinbefore. When it is desired to obtain the free base from the salt, the salt may be treated with a suitable base, for example, an 5 organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine, N-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene, or, for example, an alkali or alkaline earth metal carbonate or hydroxide, for example sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide.

10 Protecting groups may in general be chosen from any of the groups described in the literature or known to the skilled chemist as appropriate for the protection of the group in question and may be introduced by conventional methods. Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so 15 as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Specific examples of protecting groups are given below for the sake of convenience, in which "lower", as in, for example, lower alkyl, signifies that the group to which it is applied preferably has 1-4 carbon atoms. It will be understood that these examples are not exhaustive.
20 Where specific examples of methods for the removal of protecting groups are given below these are similarly not exhaustive. The use of protecting groups and methods of deprotection not specifically mentioned are, of course, within the scope of the invention.

A carboxy protecting group may be the residue of an ester-forming aliphatic or arylaliphatic alcohol or of an ester-forming silanol (the said alcohol or silanol preferably 25 containing 1-20 carbon atoms). Examples of carboxy protecting groups include straight or branched chain (1-12C)alkyl groups (for example isopropyl, and tert-butyl); lower alkoxy- lower alkyl groups (for example methoxymethyl, ethoxymethyl and isobutoxymethyl); lower acyloxy-lower alkyl groups, (for example acetoxyethyl, propionyloxymethyl, butyryloxymethyl and pivaloyloxymethyl); lower 30 alkoxy carbonyloxy-lower alkyl groups (for example 1-methoxycarbonyloxyethyl and 1-ethoxycarbonyloxyethyl); aryl-lower alkyl groups (for example benzyl, 4-methoxybenzyl, 2-nitrobenzyl, 4-nitrobenzyl, benzhydryl and phthalidyl); tri(lower alkyl)silyl groups (for example trimethylsilyl and tert-butyldimethylsilyl); tri(lower alkyl)silyl-lower alkyl groups

(for example trimethylsilylethyl); and (2-6C)alkenyl groups (for example allyl). Methods particularly appropriate for the removal of carboxyl protecting groups include for example acid-, base-, metal- or enzymically-catalysed cleavage.

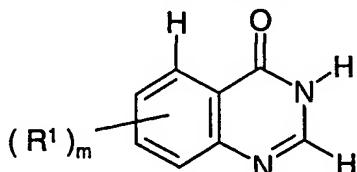
Examples of hydroxy protecting groups include lower alkyl groups (for example 5 tert-butyl), lower alkenyl groups (for example allyl); lower alkanoyl groups (for example acetyl); lower alkoxy carbonyl groups (for example tert-butoxycarbonyl); lower alkenyloxycarbonyl groups (for example allyloxycarbonyl); aryl-lower alkoxy carbonyl groups (for example benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl and 4-nitrobenzyloxycarbonyl); tri(lower alkyl)silyl (for example 10 trimethylsilyl and tert-butyldimethylsilyl) and aryl-lower alkyl (for example benzyl) groups.

Examples of amino protecting groups include formyl, aryl-lower alkyl groups (for example benzyl and substituted benzyl, 4-methoxybenzyl, 2-nitrobenzyl and 2,4-dimethoxybenzyl, and triphenylmethyl); di-4-anisylmethyl and furylmethyl groups; lower alkoxy carbonyl (for example tert-butoxycarbonyl); lower alkenyloxycarbonyl (for example 15 allyloxycarbonyl); aryl-lower alkoxy carbonyl groups (for example benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl and 4-nitrobenzyloxycarbonyl); trialkylsilyl (for example trimethylsilyl and tert-butyldimethylsilyl); alkylidene (for example methylidene) and benzylidene and substituted benzylidene groups.

Methods appropriate for removal of hydroxy and amino protecting groups include, for 20 example, acid-, base-, metal- or enzymically-catalysed hydrolysis for groups such as 2-nitrobenzyloxycarbonyl, hydrogenation for groups such as benzyl and photolytically for groups such as 2-nitrobenzyloxycarbonyl.

The reader is referred to Advanced Organic Chemistry, 4th Edition, by J. March, published by John Wiley & Sons 1992, for general guidance on reaction conditions and 25 reagents and to Protective Groups in Organic Synthesis, 2nd Edition, by T. Green *et al.*, also published by John Wiley & Son, for general guidance on protecting groups.

Quinazoline starting materials of the Formula II may be obtained by conventional procedures. For example, a 3,4-dihydroquinazolin-4-one of Formula IV



wherein m and R¹ have any of the meanings defined hereinbefore except that any functional group is protected if necessary, may be reacted with a halogenating agent such as thionyl chloride, phosphoryl chloride or a mixture of carbon tetrachloride and triphenylphosphine whereafter any protecting group that is present is removed by conventional means.

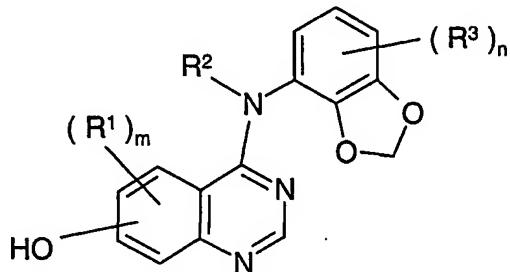
5 The 4-chloroquinazoline so obtained may be converted, if required, into a 4-pentafluorophenoxyquinazoline by reaction with pentafluorophenol in the presence of a suitable base such as potassium carbonate and in the presence of a suitable solvent such as N,N-dimethylformamide.

2,3-Methylenedioxyaniline starting materials of the Formula III may be obtained by 10 conventional procedures as illustrated in the Examples.

(b) For the production of those compounds of the Formula I wherein at least one R¹ group is a group of the formula



wherein Q¹ is an aryl-(1-6C)alkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl-(1-6C)alkyl or heterocyclyl-(1-6C)alkyl group or an optionally substituted alkyl group and X¹ is an oxygen atom, the coupling, conveniently in the presence of a suitable dehydrating agent, of a quinazoline of the Formula V



V

wherein m, R¹, R², n and R³ have any of the meanings defined hereinbefore except that any 20 functional group is protected if necessary, with an appropriate alcohol wherein any functional group is protected if necessary whereafter any protecting group that is present is removed by conventional means.

A suitable dehydrating agent is, for example, a carbodiimide reagent such as dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or a mixture of 25 an azo compound such as diethyl or di-tert-butyl azodicarboxylate and a phosphine such as triphenylphosphine. The reaction is conveniently carried out in the presence of a suitable inert

solvent or diluent, for example a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride and at a temperature in the range, for example, 10 to 150°C, preferably at or near ambient temperature.

The reaction is conveniently carried out in the presence of a suitable inert solvent or
5 diluent, for example a halogenated solvent such as methylene chloride, chloroform or carbon
tetrachloride and at a temperature in the range, for example, 10 to 150°C, preferably at or near
ambient temperature.

(c) For the production of those compounds of the Formula I wherein R¹ is an
amino-substituted (1-6C)alkoxy group (such as 2-homopiperidin-1-yethoxy or
10 3-dimethylaminopropoxy), the reaction of a compound of the Formula I wherein R¹ is a
halogeno-substituted (1-6C)alkoxy group with a heterocyclyl compound or an appropriate
amine.

The reaction is conveniently carried out in the presence of a suitable inert diluent or
carrier as defined hereinbefore and at a temperature in the range 10 to 150°C, preferably at or
15 near ambient temperature.

(d) For the production of those compounds of the Formula I wherein R¹ is a hydroxy
group, the cleavage of a quinazoline derivative of the Formula I wherein R¹ is a (1-6C)alkoxy
or arylmethoxy group.

The cleavage reaction may conveniently be carried out by any of the many procedures
20 known for such a transformation. The cleavage reaction of a compound of the Formula I
wherein R¹ is a (1-6C)alkoxy group may be carried out, for example, by treatment of the
quinazoline derivative with an alkali metal (1-6C)alkylsulphide such as sodium ethanethiolate
or, for example, by treatment with an alkali metal diarylphosphide such as lithium
25 diphenylphosphide. Alternatively the cleavage reaction may conveniently be carried out, for
example, by treatment of the quinazoline derivative with a boron or aluminium trihalide such
as boron tribromide. The cleavage reaction of a compound of the Formula I wherein R¹ is a
arylmethoxy group may be carried out, for example, by hydrogenation of the quinazoline
derivative in the presence of a suitable metallic catalyst such as palladium or by reaction with
an organic or inorganic acid, for example trifluoroacetic acid. Such reactions are preferably
30 carried out in the presence of a suitable inert solvent or diluent as defined hereinbefore and at
a temperature in the range, for example, 10 to 150°C, preferably at or near ambient
temperature.

(e) For the production of those compounds of the Formula I wherein an R¹ group contains a primary or secondary amino group, the cleavage of the corresponding compound of the Formula I wherein the R¹ group contains a protected primary or secondary amino group.

Suitable protecting groups for an amino group are, for example, any of the protecting groups disclosed hereinbefore for an amino group. Suitable methods for the cleavage of such amino protecting groups are also disclosed hereinbefore. In particular, a suitable protecting group is a lower alkoxy carbonyl group such as a tert-butoxycarbonyl group which may be cleaved under conventional reaction conditions such as under acid-catalysed hydrolysis, for example in the presence of trifluoroacetic acid.

10 (f) For the production of those compounds of the Formula I wherein an R¹ group contains a (1-6C)alkoxy or substituted (1-6C)alkoxy group or a (1-6C)alkylamino or substituted (1-6C)alkylamino group, the alkylation, conveniently in the presence of a suitable base as defined hereinbefore, of a quinazoline derivative of the formula I wherein the R¹ group contains a hydroxy group or a primary or secondary amino group as appropriate.

15 A suitable alkylating agent is, for example, any agent known in the art for the alkylation of hydroxy to alkoxy or substituted alkoxy, or for the alkylation of amino to alkylamino or substituted alkylamino, for example an alkyl or substituted alkyl halide, for example a (1-6C)alkyl chloride, bromide or iodide or a substituted (1-6C)alkyl chloride, bromide or iodide, conveniently in the presence of a suitable base as defined hereinbefore, in a 20 suitable inert solvent or diluent as defined hereinbefore and at a temperature in the range, for example, 10 to 140°C, conveniently at or near ambient temperature.

Conveniently for the production of those compounds of the Formula I wherein R¹ contains a (1-6C)alkylamino or substituted (1-6C)alkylamino group, a reductive amination reaction may be employed. For example, for the production of those compounds of the 25 Formula I wherein R¹ contains a N-methyl group, the corresponding compound containing a N-H group may be reacted with formaldehyde in the presence of a suitable reducing agent. A suitable reducing agent is, for example, a hydride reducing agent, for example an alkali metal aluminium hydride such as lithium aluminium hydride or, preferably, an alkali metal borohydride such as sodium borohydride, sodium cyanoborohydride, sodium 30 triethylborohydride, sodium trimethoxyborohydride and sodium triacetoxyborohydride. The reaction is conveniently performed in a suitable inert solvent or diluent, for example tetrahydrofuran and diethyl ether for the more powerful reducing agents such as lithium aluminium hydride, and, for example, methylene chloride or a protic solvent such as methanol

and ethanol for the less powerful reducing agents such as sodium triacetoxyborohydride and sodium cyanoborohydride. The reaction is performed at a temperature in the range, for example, 10 to 80°C, conveniently at or near ambient temperature.

(g) For the production of those compounds of the Formula I wherein R¹ is an 5 amino-hydroxy-disubstituted (1-6C)alkoxy group (such as 2-hydroxy-3-pyrrolidin-1-ylpropoxy or 3-[N-allyl-N-methylamino]-2-hydroxypropoxy), the reaction of a compound of the Formula I wherein the R¹ group contains an epoxy-substituted (1-6C)alkoxy group with a heterocyclyl compound or an appropriate amine.

The reaction is conveniently carried out in the presence of a suitable inert diluent or 10 carrier as defined hereinbefore and at a temperature in the range 10 to 150°C, preferably at or near ambient temperature.

(h) For the production of those compounds of the Formula I wherein an R¹ group contains a hydroxy group, the cleavage of the corresponding compound of the Formula I wherein the R¹ group contains a protected hydroxy group.

15 Suitable protecting groups for a hydroxy group are, for example, any of the protecting groups disclosed hereinbefore. Suitable methods for the cleavage of such hydroxy protecting groups are also disclosed hereinbefore. In particular, a suitable protecting group is a lower alkanoyl group such as an acetyl group which may be cleaved under conventional reaction conditions such as under base-catalysed conditions, for example in the presence of ammonia.

20 When a pharmaceutically-acceptable salt of a quinazoline derivative of the Formula I is required, for example an acid-addition salt, it may be obtained by, for example, reaction of said quinazoline derivative with a suitable acid using a conventional procedure.

Biological Assays

The following assays can be used to measure the effects of the compounds of the 25 present invention as c-Src tyrosine kinase inhibitors, as inhibitors in vitro of the proliferation of c-Src transfected fibroblast cells, as inhibitors in vitro of the migration of A549 human lung tumour cells and as inhibitors in vivo of the growth in nude mice of xenografts of A549 tissue.

(a) In Vitro Enzyme Assay

The ability of test compounds to inhibit the phosphorylation of a tyrosine containing 30 polypeptide substrate by the enzyme c-Src kinase was assessed using a conventional Elisa assay.

A substrate solution [100 μ l of a 20 μ g/ml solution of the polyamino acid Poly(Glu, Tyr) 4:1 (Sigma Catalogue No. P0275) in phosphate buffered saline (PBS) containing 0.2mg/ml of sodium azide] was added to each well of a number of Nunc 96-well immunoplates (Catalogue No. 439454) and the plates were sealed and stored at 4°C for 5 16 hours. The excess of substrate solution was discarded, and aliquots of Bovine Serum Albumin (BSA; 150 μ l of a 5% solution in PBS) were transferred into each substrate-coated assay well and incubated for 1 hour at ambient temperature to block non specific binding. The assay plate wells were washed in turn with PBS containing 0.05% v/v Tween 20 (PBST) and with Hepes pH7.4 buffer (50mM, 300 μ l/well) before being blotted dry.

10 Each test compound was dissolved in dimethyl sulphoxide and diluted with distilled water to give a series of dilutions (from 100 μ M to 0.001 μ M). Portions (25 μ l) of each dilution of test compound were transferred to wells in the washed assay plates. "Total" control wells contained diluted DMSO instead of compound. Aliquots (25 μ l) of an aqueous magnesium chloride solution (80mM) containing adenosine-5'-triphosphate (ATP; 40 μ M) was added to 15 all test wells except the "blank" control wells which contained magnesium chloride without ATP.

Active human c-Src kinase (recombinant enzyme expressed in Sf9 insect cells; obtained from Upstate Biotechnology Inc. product 14-117) was diluted immediately prior to use by a factor of 1:10,000 with an enzyme diluent which comprised 100mM Hepes pH7.4 20 buffer, 0.2mM sodium orthovanadate, 2mM dithiothreitol and 0.02% BSA. To start the reactions, aliquots (50 μ l) of freshly diluted enzyme were added to each well and the plates were incubated at ambient temperature for 20 minutes. The supernatant liquid in each well was discarded and the wells were washed twice with PBST. Mouse IgG anti-phosphotyrosine antibody (Upstate Biotechnology Inc. product 05-321; 100 μ l) was diluted by a factor of 25 1:6000 with PBST containing 0.5% w/v BSA and added to each well. The plates were incubated for 1 hour at ambient temperature. The supernatant liquid was discarded and each well was washed with PBST (x4). Horse radish peroxidase (HRP)-linked sheep anti-mouse Ig antibody (Amersham Catalogue No. NXA 931; 100 μ l) was diluted by a factor of 1:500 with PBST containing 0.5% w/v BSA and added to each well. The plates were incubated for 30 1 hour at ambient temperature. The supernatant liquid was discarded and the wells were washed with PBST (x4).

A PCSB capsule (Sigma Catalogue No. P4922) was dissolved in distilled water (100ml) to provide phosphate-citrate pH5 buffer (50mM) containing 0.03% sodium perborate. An aliquot (50ml) of this buffer was mixed with a 50mg tablet of 2,2'-azinobis(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS; Boehringer Catalogue No. 1204 521). Aliquots (100µl) of the resultant solution were added to each well. The plates were incubated for 20 to 60 minutes at ambient temperature until the optical density value of the "total" control wells, measured at 405nm using a plate reading spectrophotometer, was approximately 1.0. "Blank" (no ATP) and "total" (no compound) control values were used to determine the dilution range of test compound which gave 50% inhibition of enzyme activity.

10 (b) In Vitro c-Src transfected NIH 3T3 (c-src 3T3) Fibroblast Proliferation Assay

This assay determined the ability of a test compound to inhibit the proliferation of National Institute of Health (NIH) mouse 3T3 fibroblast cells that had been stably-transfected with an activating mutant (Y530F) of human c-Src.

Using a similar procedure to that described by Shalloway *et al.*, Cell, 1987, 49, 65-73, NIH 3T3 cells were transfected with an activating mutant (Y530F) of human c-Src. The resultant c-Src 3T3 cells were typically seeded at 1.5×10^4 cells per well into 96-well tissue-culture-treated clear assay plates (Costar) each containing an assay medium comprising Dulbecco's modified Eagle's medium (DMEM; Sigma) plus 0.5% foetal calf serum (FCS), 2mM glutamine, 100 units/ml penicillin and 0.1mg/ml streptomycin in 0.9% aqueous sodium chloride solution. The plates were incubated overnight at 37°C in a humidified (7.5% CO₂ : 95% air) incubator.

Test compounds were solubilised in DMSO to form a 10mM stock solution. Aliquots of the stock solution were diluted with the DMEM medium described above and added to appropriate wells. Serial dilutions were made to give a range of test concentrations. Control wells to which test compound was not added were included on each plate. The plates were incubated overnight at 37°C in a humidified (7.5% CO₂ : 95% air) incubator.

BrdU labelling reagent (Boehringer Mannheim Catalogue No. 647 229) was diluted by a factor of 1:100 in DMEM medium containing 0.5% FCS and aliquots (20µl) were added to each well to give a final concentration of 10µM. The plates were incubated at 37°C for 30 2 hours. The medium was decanted. A denaturing solution (FixDenat solution, Boehringer Mannheim Catalogue No. 647 229; 50µl) was added to each well and the plates were placed on a plate shaker at ambient temperature for 45 minutes. The supernatant was decanted and

the wells were washed with PBS (200µl per well). Anti-BrdU-Peroxidase solution (Boehringer Mannheim Catalogue No. 647 229) was diluted by a factor of 1:100 in PBS containing 1% BSA and 0.025% dried skimmed milk (Marvel (registered trade mark), Premier Beverages, Stafford, GB) and an aliquot (100µl) of the resultant solution was added to each 5 well. The plates were placed on a plate shaker at ambient temperature for 90 minutes. The wells were washed with PBS (x5) to ensure removal of non bound antibody conjugate. The plates were blotted dry and tetramethylbenzidine substrate solution (Boehringer Mannheim Catalogue No. 647 229; 100µl) was added to each well. The plates were gently agitated on a plate shaker while the colour developed during a 10 to 20 minute period. The absorbance of 10 the wells was measured at 690nm. The extent of inhibition of cellular proliferation at a range of concentrations of each test compound was determined and an anti-proliferative IC₅₀ value was derived.

(c) In Vitro Microdroplet Migration Assay

This assay determines the ability of a test compound to inhibit the migration of 15 adherent mammalian cell lines, for example the human tumour cell line A549.

RPMI medium(Sigma) containing 10% FCS, 1% L-glutamine and 0.3% agarose (Difco Catalogue No. 0142-01) was warmed to 37°C in a water bath. A stock 2% aqueous agar solution was autoclaved and stored at 42°C. An aliquot (1.5 ml) of the agar solution was added to RPMI medium (10 ml) immediately prior to its use. A549 cells (Accession No. 20 ATCC CCL185) were suspended at a concentration of 2 x 10⁷ cells/ml in the medium and maintained at a temperature of 37°C.

A droplet (2µl) of the cell/agarose mixture was transferred by pipette into the centre of each well of a number of 96-well, flat bottomed non-tissue-culture-treated microtitre plate (Bibby Sterilin Catalogue No. 642000). The plates were placed briefly on ice to speed the 25 gelling of the agarose-containing droplets. Aliquots (90µl) of medium which had been cooled to 4°C were transferred into each well, taking care not to disturb the microdroplets. Test compounds were diluted from a 10mM stock solution in DMSO using RPMI medium as described above. Aliquots (10µl) of the diluted test compounds were transferred to the wells, again taking care not to disturb the microdroplets. The plates were incubated at 37°C in a 30 humidified (7.5% CO₂ : 95% air) incubator for about 48 hours.

Migration was assessed visually and the distance of migration was measured back to the edge of the agar droplet. A migratory inhibitory IC₅₀ was derived by plotting the mean migration measurement against test compound concentration.

(d) In Vivo A549 Xenograft Growth Assay

5 This test measures the ability of compounds to inhibit the growth of the A549 human carcinoma grown as a tumour in athymic nude mice (Alderley Park nu/nu strain). A total of about 5×10^6 A549 cells in matrigel (Beckton Dickinson Catalogue No. 40234) were injected subcutaneously into the left flank of each test mouse and the resultant tumours were allowed to grow for about 14 days. Tumour size was measured twice weekly using callipers and a 10 theoretical volume was calculated. Animals were selected to provide control and treatment groups of approximately equal average tumour volume. Test compounds were prepared as a ball-milled suspension in 1% polysorbate vehicle and dosed orally once daily for a period of about 28 days. The effect on tumour growth was assessed.

Although the pharmacological properties of the compounds of the Formula I vary with 15 structural change as expected, in general activity possessed by compounds of the Formula I, may be demonstrated at the following concentrations or doses in one or more of the above tests (a), (b), (c) and (d):-

- Test (a):- IC₅₀ in the range, for example, 0.001 - 10 μM ;
- Test (b):- IC₅₀ in the range, for example, 0.01 - 20 μM ;
- 20 Test (c):- activity in the range, for example, 0.01-25 μM ;
- Test (d):- activity in the range, for example, 1-200 mg/kg/day;.

No physiologically-unacceptable toxicity was observed in Test (d) at the effective dose for compounds tested of the present invention. Accordingly no untoward toxicological effects are expected when a compound of Formula I, or a pharmaceutically-acceptable salt thereof, as 25 defined hereinbefore is administered at the dosage ranges defined hereinafter.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

30 The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for

example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

5 The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

The amount of active ingredient that is combined with one or more excipients to
10 produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 0.5 g of active agent (more suitably from 0.5 to 100 mg, for example from 1 to 30 mg) compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98
15 percent by weight of the total composition.

The size of the dose for therapeutic or prophylactic purposes of a compound of the Formula I will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine.

20 In using a compound of the Formula I for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.1 mg/kg to 75 mg/kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.1 mg/kg to 30 mg/kg body weight will
25 generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.05 mg/kg to 25 mg/kg body weight will be used. Oral administration is however preferred, particularly in tablet form. Typically, unit dosage forms will contain about 0.5 mg to 0.5 g of a compound of this invention.

According to a further aspect of the invention there is provided a quinazoline
30 derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore for use in a method of treatment of the human or animal body by therapy.

As stated above, it is known that the predominant role of c-Src non-receptor tyrosine kinase is to regulate cell motility which is necessarily required for a localised tumour to

progress through the stages of dissemination into the blood stream, invasion of other tissues and initiation of metastatic tumour growth. We have found that the quinazoline derivatives of the present invention possess potent anti-tumour activity which it is believed is obtained by way of inhibition of one or more of the non-receptor tyrosine-specific protein kinases such as 5 c-Src kinase that are involved in the signal transduction steps which lead to the invasiveness and migratory ability of metastasising tumour cells.

Accordingly the quinazoline derivatives of the present invention are of value as anti-tumour agents, in particular as selective inhibitors of the motility, dissemination and invasiveness of mammalian cancer cells leading to inhibition of metastatic tumour growth.
10 Particularly, the quinazoline derivatives of the present invention are of value as anti-invasive agents in the containment and/or treatment of solid tumour disease. Particularly, the compounds of the present invention are expected to be useful in the prevention or treatment of those tumours which are sensitive to inhibition of one or more of the multiple non-receptor tyrosine kinases such as c-Src kinase that are involved in the signal transduction steps which
15 lead to the invasiveness and migratory ability of metastasising tumour cells. Further, the compounds of the present invention are expected to be useful in the prevention or treatment of those tumours which are mediated alone or in part by inhibition of the enzyme c-Src, *i.e.* the compounds may be used to produce a c-Src enzyme inhibitory effect in a warm-blooded animal in need of such treatment. Specifically, the compounds of the present invention are
20 expected to be useful in the prevention or treatment of solid tumour disease.

Thus according to this aspect of the invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use as an anti-invasive agent in the containment and/or treatment of solid tumour disease.

25 According to a further feature of this aspect of the invention there is provided a method for producing an anti-invasive effect by the containment and/or treatment of solid tumour disease in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

30 According to a further aspect of the invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the prevention or treatment of solid tumour disease in a warm-blooded animal such as man.

According to a further feature of this aspect of the invention there is provided a method for the prevention or treatment of solid tumour disease in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a
5 pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further aspect of the invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the prevention or treatment of those tumours which are sensitive to inhibition of non-receptor tyrosine kinases
10 such as c-Src kinase that are involved in the signal transduction steps which lead to the invasiveness and migratory ability of metastasising tumour cells.

According to a further feature of this aspect of the invention there is provided a method for the prevention or treatment of those tumours which are sensitive to inhibition of non-receptor tyrosine kinases such as c-Src kinase that are involved in the signal transduction
15 steps which lead to the invasiveness and migratory ability of metastasising tumour cells which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further aspect of the invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as
20 defined hereinbefore in the manufacture of a medicament for use in providing a c-Src kinase inhibitory effect.

According to a further feature of this aspect of the invention there is provided a method for providing a c-Src kinase inhibitory effect which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a
25 pharmaceutically-acceptable salt thereof, as defined hereinbefore.

The anti-invasive treatment defined hereinbefore may be applied as a sole therapy or may involve, in addition to the quinazoline derivative of the invention, conventional surgery or radiotherapy or chemotherapy. Such chemotherapy may include one or more of the following categories of anti-tumour agents :-

- 30 (i) other anti-invasion agents (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function);
(ii) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, carboplatin, cyclophosphamide,

nitrogen mustard, melphalan, chlorambucil, busulphan and nitrosoureas); antimetabolites (for example antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside and hydroxyurea, or, for example, one of the preferred antimetabolites disclosed in European Patent Application No. 562734 such as

- 5 (2S)-2-{ α -fluoro-p-[N-(2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzamido}-4-(tetrazol-5-yl)butyric acid); antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol 10 and taxotere); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin);
- (iii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene and iodoxyfene), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example 15 goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5 α -reductase such as finasteride;
- (iv) inhibitors of growth factor function, for example such inhibitors include growth factor antibodies, growth factor receptor antibodies, tyrosine kinase inhibitors and serine/threonine 20 kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example the EGFR tyrosine kinase inhibitors N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (ZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (CP 358774) and 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)), for example 25 inhibitors of the platelet-derived growth factor family and for example inhibitors of the hepatocyte growth factor family; and
- (v) antiangiogenic agents such as those which inhibit vascular endothelial growth factor such as the compounds disclosed in International Patent Applications WO 97/22596, WO 97/30035, WO 97/32856 and WO 98/13354 and those that work by other mechanisms 30 (for example linomide, inhibitors of integrin $\alpha v \beta 3$ function and angiostatin).

Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. Such combination products

employ the compounds of this invention within the dosage range described hereinbefore and the other pharmaceutically-active agent within its approved dosage range.

According to this aspect of the invention there is provided a pharmaceutical product comprising a quinazoline derivative of the formula I as defined hereinbefore and an additional 5 anti-tumour agent as defined hereinbefore for the conjoint treatment of cancer.

Although the compounds of the Formula I are primarily of value as therapeutic agents for use in warm-blooded animals (including man), they are also useful whenever it is required to inhibit the effects of c-Src. Thus, they are useful as pharmacological standards for use in the development of new biological tests and in the search for new pharmacological agents.

10 The invention will now be illustrated in the following Examples in which, generally:

- (i) operations were carried out at ambient temperature, *i.e.* in the range 17 to 25°C and under an atmosphere of an inert gas such as argon unless otherwise stated;
- (ii) evaporations were carried out by rotary evaporation *in vacuo* and work-up procedures were carried out after removal of residual solids by filtration;

15 (iii) column chromatography (by the flash procedure) and medium pressure liquid chromatography (MPLC) were performed on Merck Kieselgel silica (Art. 9385) or Merck Lichroprep RP-18 (Art. 9303) reversed-phase silica obtained from E. Merck, Darmstadt, Germany or high pressure liquid chromatography (HPLC) was performed on C18 reverse phase silica, for example on a Dynamax C-18 60Å preparative reversed-phase column;

20 (iv) yields, where present, are not necessarily the maximum attainable;

(v) in general, the end-products of the Formula I have satisfactory microanalyses and their structures were confirmed by nuclear magnetic resonance (NMR) and/or mass spectral techniques; fast-atom bombardment (FAB) mass spectral data were obtained using a Platform spectrometer and, where appropriate, either positive ion data or negative ion data were 25 collected; NMR chemical shift values were measured on the delta scale [proton magnetic resonance spectra were determined using a Jeol JNM EX 400 spectrometer operating at a field strength of 400MHz, Varian Gemini 2000 spectrometer operating at a field strength of 300MHz or a Bruker AM300 spectrometer operating at a field strength of 300MHz]; the following abbreviations have been used: s, singlet; d, doublet; t, triplet; q, quartet; m, 30 multiplet; br, broad;

- (vi) intermediates were not generally fully characterised and purity was assessed by thin layer chromatographic, HPLC, infra-red (IR) and/or NMR analysis;

(vii) melting points are uncorrected and were determined using a Mettler SP62 automatic melting point apparatus or an oil-bath apparatus; melting points for the end-products of the Formula I were determined after crystallisation from a conventional organic solvent such as ethanol, methanol, acetone, ether or hexane, alone or in admixture;

5 (viii) the following abbreviations have been used:-

DMF	<u>N,N</u> -dimethylformamide
DMSO	dimethylsulphoxide
THF	tetrahydrofuran

Example 1**6-methoxy-4-(2,3-methylenedioxyanilino)-7-(3-morpholinopropoxy)quinazoline**

A mixture of 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (0.1 g), 2,3-methylenedioxyaniline (0.048 g), pentan-2-ol (5 ml) and a solution of hydrogen chloride in isopropanol (6M, 4 drops) was stirred and heated to 100°C for 5 hours. The resultant mixture was cooled to ambient temperature and the precipitate was isolated by filtration, washed with pentan-2-ol and dried under vacuum. There was thus obtained the title compound (0.138 g) as a dihydrochloride salt; NMR Spectrum: (DMSO_d₆ and CF₃COOD) 2.35 (m, 2H), 2.5 (m, 2H), 3.15 (m, 2H), 3.3 (m, 2H), 3.55 (d, 2H), 3.8 (t, 2H), 4.05 (s, 3H); 10 4.35 (t, 2H), 6.1 (s, 2H), 7.0 (m, 3H), 7.4 (s, 1H), 8.2 (s, 1H), 8.85 (s, 1H); Mass Spectrum: M+H⁺ 439; Elemental Analysis: Found C, 52.8; H, 5.56; N, 10.68; C₂₃H₂₆N₄O₅ 2HCl 0.5H₂O requires C, 53.08; H, 5.62; N, 10.77%.

The 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline used as a starting material was prepared as follows :-

15 A mixture of 2-amino-4-benzyloxy-5-methoxybenzamide (*J. Med. Chem.*, 1977, **20**, 146-149; 10 g), (3-dimethylamino-2-azaprop-2-en-1-ylidene)dimethylammonium chloride (Gold's reagent, 7.4 g) and dioxane (100 ml) was stirred and heated to reflux for 24 hours. Sodium acetate (3.02 g) and acetic acid (1.65 ml) were added and the reaction mixture was heated for a further 3 hours. The mixture was evaporated and water was added to the residue. 20 The resultant solid was collected by filtration, washed with water and dried. The material was recrystallised from acetic acid to give 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (8.7 g).

After repetition of the reaction so described, a mixture of 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (35 g), thionyl chloride (440 ml) and DMF (1.75 ml) was heated 25 to reflux for 4 hours. The thionyl chloride was evaporated under vacuum and the residue was azeotroped with toluene three times. The residue was dissolved in N-methylpyrrolidin-2-one (250 ml) to give a solution of 7-benzyloxy-4-chloro-6-methoxyquinazoline.

Phenol (29.05 g) was dissolved in N-methylpyrrolidin-2-one (210 ml) and sodium hydride (60% dispersion in mineral oil; 11.025 g) was added in portions with cooling. The 30 resultant mixture was stirred at ambient temperature for 3 hours. The resultant viscous suspension was diluted with N-methylpyrrolidin-2-one (180 ml) and stirred overnight. The above-mentioned solution of 7-benzyloxy-4-chloro-6-methoxyquinazoline was added and the resultant suspension was stirred and heated to 100°C for 2.5 hours. The mixture was allowed

to cool to ambient temperature and poured into water (1.5 L) with vigorous stirring. The precipitate was collected by filtration, washed with water and dried under vacuum. The material so obtained was dissolved in methylene chloride and the solution was washed with brine and filtered through phase separating paper. The solution was evaporated under vacuum
5 and the resultant residue was triturated under diethyl ether. There was thus obtained 7-benzyloxy-6-methoxy-4-phenoxyquinazoline (87.8 g); NMR Spectrum: (CDCl₃) 4.09 (s, 3H), 5.34 (s, 2H), 7.42 (m, 12H), 7.63 (s, 1H).

A mixture of a portion (36.95 g) of the material so obtained and trifluoroacetic acid (420 ml) was heated to reflux for 3 hours. The reaction mixture was allowed to cool and
10 evaporated under vacuum. The residue was stirred mechanically under water, basified by the addition of a saturated aqueous sodium bicarbonate solution and stirred overnight. The water was decanted and the residual solid was suspended in acetone. After stirring, the white solid was collected by filtration, washed with acetone and dried to give 7-hydroxy-6-methoxy-4-phenoxyquinazoline (26.61 g); NMR Spectrum: (DMSO_d₆) 3.97 (s, 3H), 7.22 (s, 1H), 7.3
15 (m, 3H), 7.47 (t, 2H), 7.56 (s, 1H), 8.47 (s, 1H), 10.7 (s, 1H).

A mixture of 7-hydroxy-6-methoxy-4-phenoxyquinazoline (25.27 g), 3-morpholinopropyl chloride (18.48 g), potassium carbonate (39.1 g) and DMF (750 ml) was stirred and heated to 90°C for 3 hours. The mixture was allowed to cool to ambient temperature and filtered. The filtrate was evaporated and the residue was triturated under
20 ethyl acetate. There was thus obtained 6-methoxy-7-(3-morpholinopropoxy)-4-phenoxyquinazoline (31.4 g); NMR Spectrum: (DMSO_d₆) 1.97 (m, 2H), 2.39 (t, 4H), 2.47 (t, 2H), 3.58 (t, 4H), 3.95 (s, 3H), 4.23 (t, 2H), 7.31 (m, 3H), 7.36 (s, 1H), 7.49 (t, 2H), 7.55 (s, 1H), 8.52 (s, 1H).

A mixture of the material so obtained and 6N aqueous hydrochloric acid solution
25 (800 ml) was stirred and heated to reflux for 1.5 hours. The reaction mixture was decanted and concentrated to a volume of 250 ml. The mixture was basified to pH9 by the addition of a saturated aqueous sodium bicarbonate solution and extracted with methylene chloride (4x400 ml). The combined extracts were filtered through phase separating paper and the filtrate was evaporated. The resultant solid was triturated under ethyl acetate to give
30 6-methoxy-7-(3-morpholinopropoxy)-3,4-dihydroquinazolin-4-one (23.9 g); NMR Spectrum: (DMSO_d₆) 1.91 (m, 2H), 2.34 (t, 4H), 2.42 (t, 2H), 3.56 (t, 4H), 3.85 (s, 3H), 4.12 (t, 2H), 7.11 (s, 1H), 7.42 (s, 1H), 7.96 (s, 1H), 12.01 (s, 1H).

A mixture of the material so obtained, thionyl chloride (210 ml) and DMF (1.8 ml) was heated to reflux for 1.5 hours. The thionyl chloride was removed by evaporation under vacuum and the residue was azeotroped with toluene three times. The residue was taken up in water and basified to pH8 by the addition of a saturated aqueous sodium bicarbonate solution.

- 5 The resultant aqueous layer was extracted with methylene chloride (4x400 ml). The combined extracts were washed with water and with brine and dried over magnesium sulphate. The solution was filtered and evaporated. The resultant solid was triturated under ethyl acetate to give 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (17.39 g);
NMR Spectrum: (CDCl₃) 2.1-2.16 (m, 2H), 2.48 (br s, 4H), 2.57 (t, 2H), 3.73 (t, 4H), 4.05 (s, 10 3H), 4.29 (t, 2H), 7.36 (s, 1H), 7.39 (s, 1H), 8.86 (s, 1H).

The 3-morpholinopropyl chloride used as a reagent was obtained as follows :-

- A mixture of morpholine (52.2 ml), 1-bromo-3-chloropropane (30 ml) and toluene (180 ml) was heated to 70°C for 3 hours. The solid was removed by filtration and the filtrate was evaporated under vacuum. The resultant oil was decanted from the additional solid which 15 was deposited and the oil was purified by vacuum distillation to yield 3-morpholinopropyl chloride (37.91 g); NMR Spectrum: (DMSO-d₆) 1.85 (m, 2H), 2.3 (t, 4H), 2.38 (t, 2H), 3.53 (t, 4H), 3.65 (t, 2H).

The 2,3-methylenedioxylaniline used as a starting material was prepared as follows :-

- A mixture of 2,3-dihydroxybenzoic acid (5 g), methanol (50 ml) and concentrated 20 sulphuric acid (10 drops) was stirred and heated to 60°C for 24 hours. The mixture was evaporated and the residue was taken up in ethyl acetate. The organic solution was washed with a saturated solution of sodium bicarbonate, dried over magnesium sulphate and evaporated to give methyl 2,3-dihydroxybenzoate (2.19 g); NMR Spectrum: (CDCl₃) 3.95 (s, 3H), 5.7 (s, 1H), 6.8 (t, 1H), 7.15 (d, H), 7.35 (d, H).

- 25 After repetition of the previous reaction, a mixture of methyl 2,3-dihydroxybenzoate (2.8 g), potassium fluoride (4.8 g) and DMF (45 ml) was stirred at ambient temperature for 30 minutes. Dibromomethane (1.28 ml) was added and the mixture was heated to 120°C for 3 hours. The mixture was cooled to ambient temperature, poured into water and extracted with diethyl ether. The organic phase was washed with water and with brine, dried over 30 magnesium sulphate and evaporated. The residue was purified by column chromatography using a 9:1 mixture of petroleum ether (b.p. 40-60°C) and ethyl acetate as eluent. There was thus obtained methyl 2,3-methylenedioxylaniline (2.3 g) as a solid; NMR Spectrum: (CDCl₃) 3.95 (s, 3H), 6.1 (s, 2H), 6.85 (t, 1H), 7.0 (d, 1H), 7.45 (d, 1H).

A mixture of the material so obtained, a 2N aqueous potassium hydroxide solution (15.5 ml) and methanol (40 ml) was stirred at ambient temperature for 2 hours. The solution was concentrated to about one quarter of the original volume and cooled in an ice bath. The mixture was acidified to pH 3.5 by the addition of a 2N aqueous hydrochloric acid solution.

- 5 The resultant precipitate was collected by filtration and washed in turn with water and diethyl ether. There was thus obtained 2,3-methylenedioxybenzoic acid (1.87 g); NMR Spectrum: (DMSO_d₆) 6.1 (s, 1H), 6.9 (t, 1H), 7.15 (d, 1H), 7.3 (d, 1H), 13.0 (br s, 1H).

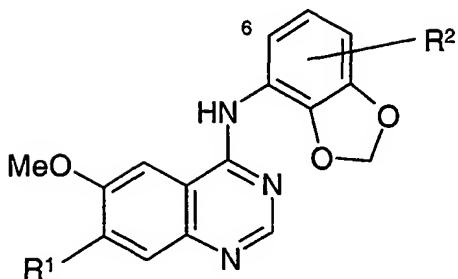
The material so obtained was suspended in anhydrous dioxane (30 ml) and anhydrous diphenylphosphoryl azide (2.45 ml), triethylamine (1.6 ml) and tert-butanol (9 ml) were 10 added. The mixture was heated to reflux for 5 hours. The mixture was cooled to ambient temperature, concentrated by evaporation and diluted with ethyl acetate. The organic phase was washed in turn with a 5% aqueous citric acid solution, water, an aqueous sodium bicarbonate solution and brine and dried over magnesium sulphate. The solvent was evaporated and the residue was purified by column chromatography on silica using a 19:1 15 mixture of petroleum ether (b.p. 40-60°C) and ethyl acetate as eluent. There was thus obtained tert-butyl 2,3-methylenedioxyphenylcarbamate (1.98 g) as a solid; NMR Spectrum: (CDCl₃) 1.55 (s, 9H), 5.95 (s, 2H), 6.4 (br s, 1H), 6.55 (d, 1H), 6.8 (t, 1H), 7.45 (d, 1H).

A 5N aqueous hydrochloric acid solution (30 ml) was added to a solution of tert-butyl 2,3-methylenedioxyphenylcarbamate (1.9 g) in ethanol (38 ml) and the reaction mixture was 20 stirred at ambient temperature for 20 hours. The ethanol was evaporated and the residual aqueous phase was washed with diethyl ether and neutralised to pH7 by the addition of solid potassium hydroxide. The resultant mixture was filtered and the aqueous phase was extracted with diethyl ether. The organic phase was washed with brine, dried over magnesium sulphate and evaporated. There was thus obtained 2,3-methylenedioxyaniline (1.0 g) as an oil; NMR 25 Spectrum: (CDCl₃) 3.0 (br s, 2H), 5.9 (s, 2H), 6.3 (m, 2H), 7.25 (t, 1H).

Example 2

Using an analogous procedure to that described in Example 1, the appropriate 4-chloroquinazoline was reacted with the appropriate 2,3-methylenedioxyaniline to give the 30 compounds described in Table I. Unless otherwise stated, each compound described in Table I was obtained as a dihydrochloride salt.

Table I



Compound No. & Note	R ¹	R ²
[1]	3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy	hydrogen
[2]	3-pyrrolidin-1-ylpropoxy	hydrogen
[3]	3-(4-methylpiperazin-1-yl)propoxy	hydrogen
[4]	3-piperidinopropoxy	hydrogen
[5]	<u>N</u> -methylpiperidin-4-ylmethoxy	hydrogen
[6]	2-[2-(4-methylpiperazin-1-yl)ethoxy]ethoxy	hydrogen
[7]	methoxy	hydrogen
[8]	benzyloxy	hydrogen
[9]	3-pyrrolidin-1-ylpropoxy	6-chloro
[10]	3-morpholinopropoxy	6-chloro
[11]	3-(4-methylpiperazin-1-yl)propoxy	6-chloro
[12]	<u>N</u> -methylpiperidin-4-ylmethoxy	6-chloro
[13]	benzyloxy	6-chloro
[14]	3-morpholinopropoxy	6-bromo
[15]	3-methylsulphonylpropoxy	6-bromo
[16]	3-morpholinopropoxy	5-methoxy
[17]	2-acetoxy-3-morpholinopropoxy	hydrogen
[18]	2-acetoxy-3-pyrrolidin-1-ylpropoxy	hydrogen
[19]	2-acetoxy-3-piperidinopropoxy	hydrogen
[20]	2-acetoxy-3-(4-cyanomethylpiperazin-1-yl)propoxy	hydrogen
[21]	2-acetoxy-3-(<u>N</u> -isopropyl- <u>N</u> -methylamino)propoxy	hydrogen
[22]	3-(4-methylpiperazin-1-yl)propoxy	5-methoxy

[23]	2-(N-methylpiperidin-4-yl)ethoxy	hydrogen
[24]	piperidin-4-ylmethoxy	hydrogen
[25]	2-piperidin-4-ylethoxy	hydrogen
[26]	N-(2-morpholinoethyl)piperidin-4-ylmethoxy	hydrogen

Notes

[1] The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃COOD) 2.35 (m, 2H), 3.45 (t, 2H), 3.75 (br s, 4H), 3.85 (br s, 4H), 4.05 (s, 3H), 4.35 (t, 5 H), 6.1 (s, 2H), 7.0 (m, 3H), 7.4 (s, 1H), 8.2 (s, 1H), 8.9 (s, 1H); Mass Spectrum: M+H⁺ 487.

The 4-chloro-7-[3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy]-6-methoxyquinazoline used as a starting material was prepared as follows :-

A mixture of 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (20.3 g), thionyl chloride (440 ml) and DMF (1.75 ml) was heated to reflux for 4 hours. The thionyl chloride 10 was evaporated under vacuum and the residue was azeotroped with toluene three times to give 7-benzyloxy-4-chloro-6-methoxyquinazoline.

A mixture of the 7-benzyloxy-4-chloro-6-methoxyquinazoline so obtained, potassium carbonate (50 g) and 4-chloro-2-fluorophenol (8.8 ml) and DMF (500 ml) was stirred and heated to 100°C for 5 hours. The mixture was allowed to cool to ambient temperature, poured 15 into water (2 L) and stirred at ambient temperature for a few minutes. The resultant solid was isolated and washed with water. The solid was dissolved in methylene chloride and the solution was filtered and treated with decolourising charcoal. The resultant solution was filtered and evaporated to give a solid which was triturated under diethyl ether. There was thus obtained 7-benzyloxy-4-(4-chloro-2-fluorophenoxy)-6-methoxyquinazoline (23.2 g); 20 NMR Spectrum: (DMSO_d₆) 3.98 (s, 3H), 5.34 (s, 2H), 7.42 (m, 9H), 7.69 (m, 1H), 8.55 (s, 1H).

A mixture of the material so obtained and trifluoroacetic acid (15 ml) was heated to reflux for 3 hours. The reaction mixture was allowed to cool, toluene was added and the mixture was evaporated. The residue was triturated under diethyl ether and then under 25 acetone. The resultant precipitate was isolated and dried to give 4-(4-chloro-2-fluorophenoxy)-7-hydroxy-6-methoxyquinazoline trifluoroacetate salt (21.8 g) which was used without further purification.

3-(1,1-Dioxotetrahydro-4H-1,4-thiazin-4-yl)propan-1-ol (4.2 g) and 1,1'-(azodicarbonyl)dipiperidine (11.7 g) were added in turn to a mixture of 4-(4-chloro-

2-fluorophenoxy)-7-hydroxy-6-methoxyquinazoline (5.0 g), tributylphosphine (11.1 ml) and methylene chloride (150 ml). The resultant mixture was stirred at ambient temperature overnight. The mixture was diluted with diethyl ether (300 ml) and the precipitate was removed by filtration. The filtrate was evaporated and the residue was purified by column chromatography on silica using a 19:1 mixture of methylene chloride and methanol as eluent. The material so obtained was triturated under ethyl acetate and dried to give 4-(4-chloro-2-fluorophenoxy)-7-[3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy]-6-methoxyquinazoline (5.4 g); NMR Spectrum: (DMSO_d₆) 1.86 (m, 2H), 2.65 (t, 2H), 2.92 (m, 4H), 3.08 (m, 4H), 3.97 (s, 3H), 4.26 (t, 2H), 7.4 (m, 1H), 7.42 (s, 1H), 7.56 (m, 2H), 7.68 (m, 1H), 8.54 (s, 1H).

A mixture of a portion (3.5 g) of the material so obtained and a 2N aqueous hydrochloric acid solution (56 ml) was stirred and heated to 95°C for 2 hours. The reaction mixture was cooled to ambient temperature and treated with solid sodium bicarbonate to give a thick paste which was diluted with water and filtered. The solid was transferred to a flask and azeotroped with toluene twice to give a dry solid. The solid was purified by column chromatography on silica using a 19:1 mixture of methylene chloride and methanol as eluent. There was thus obtained 7-[3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy]-6-methoxy-3,4-dihydroquinazolin-4-one (2.26 g) as a white solid; Mass Spectrum: M+H⁺ 368.

After repetition of the previous reaction, a mixture of 7-[3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy]-6-methoxy-3,4-dihydroquinazolin-4-one (4.2 g), thionyl chloride (45 ml) and DMF (0.1 ml) was heated to reflux for 2.5 hours. The residue was diluted with toluene and was evaporated under vacuum. The residue was taken up in water and basified to pH8 with a saturated aqueous sodium bicarbonate solution. The mixture was extracted with methylene chloride and the organic layer was washed in turn with water and brine. The organic solution was filtered through phase separating paper and evaporated to give an orange solid which was purified by column chromatography on silica using a 19:1 mixture of methylene chloride and methanol as eluent. The resultant solid was triturated under diethyl ether and dried to give 4-chloro-7-[3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy]-6-methoxyquinazoline (2.27 g); Mass Spectrum: M+H⁺ 386.

The 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propan-1-ol used as an intermediate was obtained as follows :-

A mixture of 3-aminopropan-1-ol (0.65 ml) and divinyl sulphone (1 g) was heated to 110°C for 45 minutes. The mixture was allowed to cool to ambient temperature and was

purified by column chromatography on silica using a 19:1 mixture of methylene chloride and methanol as eluent. There was thus obtained 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propan-1-ol (0.8 g); NMR Spectrum: (CDCl₃) 1.7-1.8 (m, 2H), 2.73 (t, 2H), 3.06 (br s, 8H), 3.25 (s, 1H), 3.78 (t, 2H); Mass Spectrum: M+H⁺ 194.

- 5 [2] The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃COOD) 1.8 (m, 2H), 2.05 (m, 2H), 2.3 (m, 2H), 3.05 (m, 2H), 3.35 (t, 2H), 3.6 (m, 2H), 4.0 (s, 3H), 4.3 (t, 2H), 6.1 (s, 2H), 6.95 (m, 3H), 7.4 (s, 1H), 8.2 (s, 1H), 8.85 (s, 1H); Mass Spectrum: M+H⁺ 423.

The 4-chloro-7-(3-pyrrolidin-1-ylpropoxy)-6-methoxyquinazoline used as a starting material was prepared as follows :-

A mixture of 4-hydroxy-3-methoxybenzoic acid (8.4 g), 3-(pyrrolidin-1-yl)propyl chloride (J. Amer. Chem. Soc., 1955, 77, 2272; 14.75 g), potassium carbonate (13.8 g), potassium iodide (1.66 g) and DMF (150 ml) was stirred and heated to 100°C for 3 hours. The mixture was allowed to cool to ambient temperature, filtered and the filtrate was evaporated. The residue was dissolved in ethanol (75 ml), 2N aqueous sodium hydroxide solution (75 ml) was added and the mixture was heated to 90°C for 2 hours. The mixture was concentrated by evaporation and acidified by the addition of concentrated aqueous hydrochloric acid. The resultant mixture was washed with diethyl ether and then purified by column chromatography using a Diaion (trade mark of Mitsubishi) HP20SS resin column, eluting with water and then with a gradient of methanol (0 to 25%) in dilute hydrochloric acid (pH2.2). The methanol was removed by evaporation and the aqueous residue was freeze dried to give 3-methoxy-4-(3-pyrrolidin-1-ylpropoxy)benzoic acid hydrochloride (12.2 g); NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 2.2 (m, 2H), 3.15 (t, 2H), 3.3 (t, 2H), 3.5 (d, 2H), 3.7 (t, 2H), 3.82 (s, 3H), 4.05 (d, 2H), 4.15 (t, 2H), 7.07 (d, 1H), 7.48 (s, 1H), 7.59 (d, 1H).

25 The material so obtained was dissolved in trifluoroacetic acid (40 ml) and the solution was cooled to 0°C. Fuming nitric acid (2.4 ml) was added slowly. The cooling bath was removed and the reaction mixture was stirred at ambient temperature for 1 hour. The mixture was evaporated and a mixture of ice and water was added to the residue. The mixture was evaporated. The solid residue was dissolved in dilute hydrochloric acid (pH2.2) and purified by column chromatography using a Diaion HP20SS resin column using a gradient of methanol (0 to 50%) in water. Concentration of the fractions by evaporation gave a precipitate which was collected and dried under vacuum over phosphorus pentoxide. There was thus obtained 5-methoxy-2-nitro-4-(3-pyrrolidin-1-ylpropoxy)benzoic acid hydrochloride (12.1 g, 90%);

NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 1.8-1.9 (m, 2H), 2.0-2.1 (m, 2H), 2.1-2.2 (m, 2H), 3.0-3.1 (m, 2H), 3.3 (t, 2H), 3.6-3.7 (m, 2H), 3.95 (s, 3H), 4.25 (t, 2H), 7.35 (s, 1H), 7.62 (s, 1H).

A mixture of a portion (9.63 g) of the material so obtained, thionyl chloride (20 ml)
5 and DMF (0.05 ml) was heated to 45°C for 1.5 hours. The excess thionyl chloride was
evaporated using the evaporation of added toluene (x2) to remove the last traces. The
resultant solid was suspended in a mixture of THF (250 ml) and methylene chloride (100ml)
and ammonia was bubbled though the mixture for 30 minutes. The resultant mixture was
stirred for a further 1.5 hours at ambient temperature. The volatiles were removed by
10 evaporation and the residue was dissolved in water and purified by column chromatography
using a Diaion HP20SS resin column eluting with a gradient of methanol (0 to 5%) in water.
The solvent was removed by evaporation from the fractions containing product. The residue
was dissolved in a minimum of methanol and the solution was diluted with diethyl ether. The
resultant precipitate was collected by filtration, washed with diethyl ether and dried under
15 vacuum to give 5-methoxy-2-nitro-4-(3-pyrrolidin-1-ylpropoxy)benzamide (7.23 g); NMR
Spectrum: (DMSO_d₆ and CF₃CO₂D) 1.85-1.95 (m, 2H), 2-2.1 (m, 2H), 2.15-2.25 (m, 2H),
3.0-3.1 (m, 2H), 3.31 (t, 2H), 3.62 (t, 2H), 3.93 (s, 3H), 4.2 (t, 2H), 7.16 (s, 1H), 7.6 (s, 1H).

A mixture of a portion (1.5 g) of the material so obtained, concentrated aqueous
hydrochloric acid (5 ml) and methanol (20 ml) was warmed to 50°C to give a solution. Iron
20 powder (1.3 g) was added in portions and the reaction mixture was heated to reflux for 1 hour.
The mixture was allowed to cool to ambient temperature. Insoluble material was removed by
filtration through diatomaceous earth and the filtrate was evaporated. The residue was
purified by column chromatography using a Diaion HP20SS resin column, eluting with water
and then with dilute aqueous hydrochloric acid (pH2). The fractions containing product were
25 concentrated by evaporation and the resultant precipitate was collected by filtration and dried
under vacuum over phosphorus pentoxide. There was thus obtained 2-amino-5-methoxy-
4-(3-pyrrolidin-1-ylpropoxy)benzamide hydrochloride (1.44 g); NMR Spectrum: (DMSO_d₆
and CF₃CO₂D) 1.9 (br s, 2H), 2.05 (br s, 2H), 2.2 (br s, 2H), 3.05 (br s, 2H), 3.3 (t, 2H), 3.61
(br s, 2H), 3.8 (s, 3H), 4.11 (t, 2H), 7.05 (s, 1H), 7.53 (s, 1H).

30 After repetition of the previous reaction, a mixture of 2-amino-5-methoxy-
4-(3-pyrrolidin-1-ylpropoxy)benzamide hydrochloride (5.92 g), Gold's reagent (3.5 g) and
dioxane (50 ml) was heated to reflux for 5 hours. Acetic acid (0.7 ml) and sodium acetate
(1.33 g) were added and the reaction mixture was heated to reflux for a further 5 hours. The

mixture was allowed to cool to ambient temperature and evaporated. The residue was dissolved in water, adjusted to pH8 with 2N aqueous sodium hydroxide solution and purified on a Diaion HP20SS resin column eluting with methanol (gradient 0-50 %) in water. The fractions containing product were concentrated by evaporation and then freeze dried to give

5 6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)-3,4-dihydroquinazolin-4-one (4.55 g); NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 1.9 (m, 2H), 2.0-2.1 (m, 2H), 2.2-2.3 (m, 2H), 3.05 (m, 2H), 3.34 (t, 2H), 3.6-3.7 (br s, 2H), 3.94 (s, 3H), 4.27 (t, 2H), 7.31 (s, 1H), 7.55 (s, 1H), 9.02 (s, 1H).

A mixture of a portion (1.7 g) of the material so obtained, thionyl chloride (25 ml) and
10 DMF (0.2 ml) was heated at reflux for 3 hours. Excess thionyl chloride was removed by evaporation and by azeotroping with toluene (x2). The residue was suspended in diethyl ether and washed with a 10% aqueous solution of sodium bicarbonate. The organic layer was dried over magnesium sulphate and evaporated to give 4-chloro-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (1.94 g); NMR Spectrum: (CDCl₃) 1.8 (br s, 4H), 2.17 (m, 2H), 2.6 (br s, 4H), 2.7 (t, 2H), 4.05 (s, 3H), 4.3 (t, 2H), 7.35 (s, 1H), 7.38 (s, 1H), 8.86 (s, 1H).

[3] The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃COOD) 2.35 (m, 2H), 2.9 (s, 3H), 3.3-4.0 (br s, 10H), 4.05 (s, 3H), 4.35 (m, 2H), 6.1 (s, 2H), 7.0 (m, 3H), 7.4 (s, 1H), 8.35 (s, 1H), 8.85 (s, 1H); Mass Spectrum: M+H⁺ 452.

The 4-chloro-7-[3-(4-methylpiperazin-1-yl)propoxy]-6-methoxyquinazoline used as a
20 starting material was prepared as follows :-

A mixture of 3-bromopropanol (20 ml), N-methylpiperazine (29 ml), potassium carbonate (83 g) and ethanol (200 ml) was stirred and heated to reflux for 20 hours. The mixture was cooled to ambient temperature and filtered. The filtrate was evaporated and the residue was triturated under diethyl ether. The resultant mixture was filtered and the filtrate
25 was evaporated. The residue was purified by distillation at about 60-70°C under about 0.2 mm Hg to give 1-(3-hydroxypropyl)-4-methylpiperazine (17 g); NMR Spectrum: (CDCl₃) 1.72 (m, 2H), 2.3 (s, 3H), 2.2-2.8 (m, 8H), 2.6 (t, 2H), 3.8 (t, 2H), 5.3 (br s, 1H).

4-Toluenesulphonyl chloride (3.2 g) was added to a stirred mixture of
1-(3-hydroxypropyl)-4-methylpiperazine (2.4 g), triethylamine (4.6 ml) and methylene
30 chloride (60 ml) and the resultant mixture was stirred at ambient temperature for 2 hours. The solution was washed in turn with a saturated aqueous sodium bicarbonate solution and with water and filtered through phase separating paper. The organic filtrate was evaporated to give

3-(4-methylpiperazin-1-yl)propyl 4-toluenesulphonate as an oil which crystallised on standing (3.7 g); Mass Spectrum: M+H⁺ 313.

A mixture of the trifluoroacetic acid salt of 4-(4-chloro-2-fluorophenoxy)-7-hydroxy-6-methoxyquinazoline (3.2 g), 3-(4-methylpiperazin-1-yl)propyl 4-toluenesulphonate (3.0 g), 5 potassium carbonate (6.1 g) and DMF (60 ml) was stirred at 90°C for 5 hours. The resultant mixture was cooled to ambient temperature, poured into water (700 ml) and extracted with ethyl acetate (5 times). The combined extracts were washed in turn with water, a saturated aqueous sodium bicarbonate solution, water and brine. The ethyl acetate solution was dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 100: 8:1 mixture of methylene chloride, methanol and a concentrated aqueous ammonium hydroxide solution (0.88 g/ml) as eluent. The material so obtained was triturated under diethyl ether. There was thus obtained 4-(4-chloro-2-fluorophenoxy)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline (1.64 g); NMR Spectrum: (DMSO_d₆) 1.95 (m, 2H), 2.14 (s, 3H), 2.35 (m, 8H), 2.44 (t, 2H), 3.96 (s, 15 3H), 4.22 (t, 2H), 7.38 (s, 1H), 7.4 (m, 1H), 7.54 (m, 2H), 7.68 (m, 1H), 8.55 (s, 1H).

After repetition of the previous reaction, a mixture of 4-(4-chloro-2-fluorophenoxy)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline (2.6 g) and 2N aqueous hydrochloric acid solution (45 ml) was stirred and heated to 95°C for 2 hours. The mixture was cooled to ambient temperature and basified by the addition of solid sodium bicarbonate 20 The mixture was evaporated and the residue was purified by column chromatography on silica using a 50: 8:1 mixture of methylene chloride, methanol and a concentrated aqueous ammonium hydroxide solution (0.88 g/ml) as eluent. There was thus obtained 6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]-3,4-dihydroquinazolin-4-one (1.8 g,); Mass Spectrum: M+H⁺ 333.

25 After repetition of the previous reaction, a mixture of 6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]-3,4-dihydroquinazolin-4-one (2.15 g), thionyl chloride (25 ml) and DMF (0.18 ml) was stirred and heated to reflux for 2 hours. The thionyl chloride was evaporated under vacuum and the residue azeotroped twice with toluene. The residue was taken up in water, basified by the addition of a saturated aqueous sodium bicarbonate 30 solution and extracted with methylene chloride (4 times). The combined extracts were washed in turn with water and brine and filtered through phase separating paper. The filtrate was evaporated under vacuum and the residue was purified by column chromatography on silica using a 100: 8:1 mixture of methylene chloride, methanol and a concentrated aqueous

ammonium hydroxide solution (0.88 g/ml) as eluent. The solid so obtained was triturated under acetone, filtered and dried to give 4-chloro-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline (1.2 g); Mass Spectrum: M+H⁺ 351.

[4] The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃COOD) 1.4 (m, 1H), 1.7-1.9 (m, 5H), 2.35 (m, 2H), 2.95 (m, 2H), 3.25 (m, 2H), 3.55 (m, 2H), 4.05 (s, 3H), 4.3 (t, 2H), 6.1 (s, 2H), 7.0 (m, 3H), 7.45 (s, 1H), 8.25 (s, 1H), 8.85 (s, 1H); Mass Spectrum: M+H⁺ 437.

The 4-chloro-7-(3-piperidinopropoxy)-6-methoxyquinazoline used as a starting material was prepared as follows :-

10 Sodium hydride (60% suspension in mineral oil, 1.44 g) was added portionwise during 20 minutes to a solution of 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (International Patent Application WO 97/22596, Example 1 thereof; 8.46 g) in DMF (70 ml). The mixture was stirred at ambient temperature for 1.5 hours. Chloromethyl pivalate (5.65 g) was added dropwise and the mixture was stirred at ambient temperature for 2 hours. The 15 mixture was diluted with ethyl acetate (100 ml) and poured onto a mixture (400 ml) of ice and water containing 2N aqueous hydrochloric acid (4 ml). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined extracts were washed with brine, dried over magnesium sulphate and evaporated. The residue was triturated under a mixture of diethyl ether and petroleum ether (b.p. 60-80°C) and the resultant solid was 20 collected and dried under vacuum. There was thus obtained 7-benzyloxy-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (10 g); NMR Spectrum: (DMSO_d₆) 1.11 (s, 9H), 3.89 (s, 3H), 5.3 (s, 2H), 5.9 (s, 2H), 7.27 (s, 1H), 7.35 (m, 1H), 7.47 (t, 2H), 7.49 (d, 2H), 7.51 (s, 1H), 8.34 (s, 1H).

A mixture of a portion (7 g) of the material so obtained, 10% palladium-on-charcoal 25 catalyst (0.7 g), DMF (50 ml), methanol (50 ml), acetic acid (0.7 ml) and ethyl acetate (250 ml) was stirred under an atmosphere pressure of hydrogen for 40 minutes. The catalyst was removed by filtration and the solvent was evaporated. The residue was triturated under diethyl ether and the resultant solid was collected and dried under vacuum. There was thus obtained 7-hydroxy-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (4.36 g); 30 NMR Spectrum: (DMSO_d₆) 1.1 (s, 9H), 3.89 (s, 3H), 5.89 (s, 2H), 7.0 (s, 1H), 7.48 (s, 1H), 8.5 (s, 1H).

Diethyl azodicarboxylate (3.9 ml) was added dropwise to a stirred mixture of 7-hydroxy-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (5 g),

3-bromopropanol (2.21 ml), triphenylphosphine (6.42 g) and methylene chloride (50 ml) and the mixture was stirred at ambient temperature for 2 hours. The mixture was evaporated and the residue was purified by column chromatography on silica using a 19:1 mixture of methylene chloride and methanol as eluent. There was thus obtained 7-(3-bromopropoxy)-

- 5 6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (6 g); NMR Spectrum: (DMSO_d₆) 1.12 (s, 9H), 2.32 (t, 2H), 3.7 (t, 2H), 3.9 (s, 3H), 4.25 (t, 2H), 5.9 (s, 2H), 7.2 (s, 1H), 7.61 (s, 1H), 8.36 (s, 1H).

A mixture of a portion (2.89 g) of the material so obtained and piperidine (10 ml) was stirred and heated to 100°C for 1 hour. The mixture was evaporated and the residue was
10 partitioned between methylene chloride and a saturated aqueous ammonium chloride solution. The organic phase was washed with brine, dried over magnesium sulphate and evaporated. There was thus obtained 6-methoxy-7-(3-piperidinopropoxy)-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (2.4 g); NMR Spectrum: (DMSO_d₆) 1.15 (s, 9H), 1.35-1.5 (m, 1H), 1.6-1.8 (m, 3H), 1.8-1.9 (d, 2H), 2.2-2.3 (m, 2H), 2.95 (t, 2H), 3.25 (t, 2H), 3.55 (d, 2H),
15 3.95 (s, 3H), 4.25 (t, 2H), 5.94 (s, 2H), 7.24 (s, 1H), 7.56 (s, 1H), 8.36 (s, 1H).

A mixture of the material so obtained and a 7N solution of ammonia in methanol (50 ml) was stirred at ambient temperature for 16 hours. The mixture was evaporated and the residue was triturated under diethyl ether. The resultant solid was isolated, washed in turn with diethyl ether and a 1:1 mixture of diethyl ether and methylene chloride and dried under
20 vacuum. There was thus obtained 6-methoxy-7-(3-piperidinopropoxy)-3,4-dihydroquinazolin-4-one (1.65 g); NMR Spectrum: (DMSO_d₆) 1.3-1.4 (m, 2H), 1.4-1.55 (m, 4H), 1.85-1.95 (m, 2H), 2.35 (br s, 4H), 2.4 (t, 2H), 3.9 (s, 3H), 4.15 (t, 2H), 7.11 (s, 1H), 7.44 (s, 1H), 7.9 (s, 1H).

A mixture of the material so obtained, thionyl chloride (15 ml) and DMF (1.5 ml) was
25 heated to reflux for 3 hours. The mixture was evaporated. Toluene was added and the mixture was again evaporated. The residue was partitioned between methylene chloride and a saturated aqueous sodium bicarbonate solution (the basicity of which was adjusted to pH10 by adding 6N aqueous sodium hydroxide). The organic layer was separated, washed with brine, dried over magnesium sulphate and evaporated. There was thus obtained 4-chloro-
30 6-methoxy-7-(3-piperidinopropoxy)quinazoline (1.2 g); NMR Spectrum: (DMSO_d₆) 1.35-1.45 (m, 2H), 1.5-1.6 (m, 4H), 1.9-2.05 (m, 2H), 2.4 (br s, 4H), 2.45 (t, 2H), 4.0 (s, 3H), 4.29 (t, 2H), 7.41 (s, 1H), 7.46 (s, 1H), 8.9 (s, 1H).

[5] The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃COOD) 1.6 (m, 2H), 2.05 (m, 2H), 2.15 (m, 1H), 2.75 (s, 3H), 3.05 (m, 2H), 3.5 (m, 2H), 4.0 (s, 3H), 4.15 (d, 2H), 6.1 (s, 2H), 7.0 (m, 3H), 7.4 (s, 1H), 8.2 (s, 1H), 8.85 (s, 1H); Mass Spectrum: M+H⁺ 423.

5 The 4-chloro-7-(N-methylpiperidin-4-ylmethoxy)-6-methoxyquinazoline used as a starting material was prepared as follows :-

A solution of di-tert-butyl dicarbonate (41.7 g) in ethyl acetate (75 ml) was added dropwise to a stirred solution of ethyl piperidine-4-carboxylate (30 g) in ethyl acetate (150 ml) which had been cooled to 0 to 5°C in an ice-bath. The resultant mixture was stirred at 10 ambient temperature for 48 hours. The mixture was poured into water (300 ml). The organic layer was separated, washed in turn with water (200 ml), 0.1N aqueous hydrochloric acid solution (200 ml), a saturated aqueous sodium bicarbonate solution (200 ml) and brine (200 ml), dried over magnesium sulphate and evaporated. There was thus obtained ethyl N-tert-butoxycarbonylpiperidine-4-carboxylate (48 g); NMR Spectrum: (CDCl₃) 1.25 (t, 3H), 15 1.45 (s, 9H), 1.55-1.7 (m, 2H), 1.8-2.0 (d, 2H), 2.35-2.5 (m, 1H), 2.7-2.95 (t, 2H), 3.9-4.1 (br s, 2H), 4.15 (q, 2H).

A solution of the material so obtained in THF (180 ml) was cooled at 0°C and lithium aluminium hydride (1M solution in THF; 133 ml) was added dropwise. The mixture was stirred at 0°C for 2 hours. Water (30 ml) and 2N aqueous sodium hydroxide solution (10 ml) 20 were added in turn and the mixture was stirred for 15 minutes. The resultant mixture was filtered through diatomaceous earth and the solids were washed with ethyl acetate. The filtrate was washed in turn with water and with brine, dried over magnesium sulphate and evaporated. There was thus obtained N-tert-butoxycarbonyl-4-hydroxymethylpiperidine (36.3 g); NMR Spectrum: (CDCl₃) 1.05-1.2 (m, 2H), 1.35-1.55 (m, 10H), 1.6-1.8 (m, 2H), 25 2.6-2.8 (t, 2H), 3.4-3.6 (t, 2H), 4.0-4.2 (br s, 2H).

1,4-Diazabicyclo[2.2.2]octane (42.4 g) was added to a solution of N-tert-butoxycarbonyl-4-hydroxymethylpiperidine (52.5 g) in tert-butyl methyl ether (525 ml) and the mixture was stirred at ambient temperature for 15 minutes. The mixture was then cooled in an ice-bath to 5°C and a solution of 4-toluenesulphonyl chloride (62.8 g) in 30 tert-butyl methyl ether (525 ml) was added dropwise over 2 hours while maintaining the reaction temperature at approximately 0°C. The resultant mixture was allowed to warm to ambient temperature and was stirred for 1 hour. Petroleum ether (b.p. 60-80°C, 1L) was added and the precipitate was removed by filtration. The filtrate was evaporated to give a

solid residue which was dissolved in diethyl ether. The organic solution was washed in turn with 0.5N aqueous hydrochloric acid solution, water, a saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulphate and evaporated. There was thus obtained N-tert-butoxycarbonyl-4-(4-toluenesulphonyloxymethyl)piperidine (76.7 g); NMR Spectrum: 5 (CDCl₃) 1.0-1.2 (m, 2H), 1.45 (s, 9H), 1.65 (d, 2H), 1.75-1.9 (m, 2H), 2.45 (s, 3H), 2.55-2.75 (m, 2H), 3.85 (d, 1H), 4.0-4.2 (br s, 2H), 7.35 (d, 2H), 7.8 (d, 2H).

A portion (40 g) of the material so obtained was added to a suspension of ethyl 4-hydroxy-3-methoxybenzoate (19.6 g) and potassium carbonate (28 g) in DMF (200 ml) and the resultant mixture was stirred and heated to 95°C for 2.5 hours. The mixture was cooled to 10 ambient temperature and partitioned between water and a mixture of ethyl acetate and diethyl ether. The organic layer was washed in turn with water and brine, dried over magnesium sulphate and evaporated. The resulting oil was crystallised from petroleum ether (b.p. 60-80°C) and the suspension was stored overnight at 5°C. The resultant solid was collected by filtration, washed with petroleum ether and dried under vacuum. There was thus 15 obtained ethyl 4-(N-tert-butoxycarbonylpiperidin-4-ylmethoxy)-3-methoxybenzoate (35 g), m.p. 81-83°C; NMR Spectrum: (CDCl₃) 1.2-1.35 (m, 2H), 1.4 (t, 3H), 1.48 (s, 9H), 1.8-1.9 (d, 2H), 2.0-2.15 (m, 2H), 2.75 (t, 2H), 3.9 (d, 2H), 3.95 (s, 3H), 4.05-4.25 (br s, 2H), 4.35 (q, 2H), 6.85 (d, 1H), 7.55 (s, 1H), 7.65 (d, 1H).

The material so obtained was dissolved in formic acid (35 ml), formaldehyde (12M, 20 37% in water, 35 ml) was added and the mixture was stirred and heated to 95°C for 3 hours. The resultant mixture was evaporated. The residue was dissolved in methylene chloride and hydrogen chloride (3M solution in diethyl ether; 40 ml) was added. The mixture was diluted with diethyl ether and the mixture was triturated until a solid was formed. The solid was collected, washed with diethyl ether and dried under vacuum overnight at 50°C. There was 25 thus obtained ethyl 3-methoxy-4-(N-methylpiperidin-4-ylmethoxy)benzoate (30.6 g); NMR Spectrum: (DMSO_d₆) 1.29 (t, 3H), 1.5-1.7 (m, 2H), 1.95 (d, 2H), 2.0-2.15 (br s, 1H), 2.72 (s, 3H), 2.9-3.1 (m, 2H), 3.35-3.5 (br s, 2H), 3.85 (s, 3H), 3.9-4.05 (br s, 2H), 4.3 (q, 2H), 7.1 (d, 1H), 7.48 (s, 1H), 7.6 (d, 1H).

The material so obtained was dissolved in methylene chloride (75 ml) and the solution 30 was cooled in an ice-bath to 0-5°C. Trifluoroacetic acid (37.5 ml) was added followed by the dropwise addition over 15 minutes of a solution of fuming nitric acid (24M; 7.42 ml) in methylene chloride (15 ml). The resultant solution was allowed to warm to ambient temperature and was stirred for 2 hours. Volatile materials were evaporated. The residue was

dissolved in methylene chloride (50 ml) and the solution was cooled in an ice-bath to 0-5°C. Diethyl ether was added and the resultant precipitate was collected and dried under vacuum at 50°C. The solid was dissolved in methylene chloride (500 ml) and hydrogen chloride (3M solution in diethyl ether; 30 ml) was added followed by diethyl ether (500 ml). The resultant 5 solid was collected and dried under vacuum at 50°C. There was thus obtained ethyl 5-methoxy-4-(*N*-methylpiperidin-4-ylmethoxy)-2-nitrobenzoate (28.4 g); NMR Spectrum: (DMSO-d_6) 1.3 (t, 3H), 1.45-1.65 (m, 2H), 1.75-2.1 (m, 3H), 2.75 (s, 3H), 2.9-3.05 (m, 2H), 3.4-3.5 (d, 2H), 3.95 (s, 3H), 4.05 (d, 2H), 4.3 (q, 2H), 7.32 (s, 1H), 7.66 (s, 1H).

A mixture of a portion (3.89 g) of the material so obtained, 10% platinum-on-activated 10 carbon (50% wet, 0.389 g) and methanol (80 ml) was stirred under 1.8 atmospheres pressure of hydrogen until uptake of hydrogen ceased. The mixture was filtered and the filtrate was evaporated. The residue was dissolved in water (30 ml) and basified to pH10 by the addition of a saturated aqueous sodium bicarbonate solution. The mixture was diluted with a 1:1 mixture of ethyl acetate and diethyl ether and the organic layer was separated. The aqueous 15 layer was further extracted with a 1:1 mixture of ethyl acetate and diethyl ether and the organic extracts were combined, washed in turn with water and brine, dried over magnesium sulphate and evaporated. The residue was triturated under a mixture of petroleum ether (b.p. 60-80°C) and diethyl ether. The solid so obtained was isolated, washed with petroleum ether and dried under vacuum at 60°C. There was thus obtained ethyl 2-amino-5-methoxy- 20 4-(*N*-methylpiperidin-4-ylmethoxy)benzoate (2.58 g), m.p. 111-112°C; NMR Spectrum: (CDCl_3) 1.35 (t, 3H), 1.4-1.5 (m, 2H), 1.85 (m, 3H), 1.95 (t, 2H), 2.29 (s, 3H), 2.9 (d, 2H), 3.8 (s, 3H), 3.85 (d, 2H), 4.3 (q, 2H), 5.55 (br s, 2H), 6.13 (s, 1H), 7.33 (s, 1H).

A mixture of ethyl 2-amino-5-methoxy-4-(*N*-methylpiperidin-4-ylmethoxy)benzoate (16.1 g), formamidine acetic acid salt (5.2 g) and 2-methoxyethanol (160 ml) was stirred and 25 heated at 115°C for 2 hours. Further formamidine acetic acid salt (10.4 g) was added in portions every 30 minutes during 4 hours and heating was continued for 30 minutes after the last addition. The resultant mixture was evaporated. The solid residue was stirred under a mixture of methylene chloride (50ml) and ethanol (100ml). The precipitate was removed by filtration and the filtrate was concentrated to a final volume of 100ml. The resultant 30 suspension was cooled to 5°C. The solid so obtained was collected, washed with cold ethanol and with diethyl ether and dried under vacuum at 60°C. There was thus obtained 6-methoxy-7-(*N*-methylpiperidin-4-ylmethoxy)-3,4-dihydroquinazolin-4-one (12.7 g); NMR Spectrum:

(DMSO_d₆) 1.25-1.4 (m, 2H), 1.75 (d, 2H), 1.9 (t, 1H), 1.9 (s, 3H), 2.16 (s, 2H), 2.8 (d, 2H), 3.9 (s, 3H), 4.0 (d, 2H), 7.11 (s, 1H), 7.44 (s, 1H), 7.97 (s, 1H).

A mixture of a portion (2.8 g) of the material so obtained, thionyl chloride (28 ml) and DMF (0.28 ml) was heated to reflux for 1 hour. The mixture was evaporated and the precipitate was triturated under diethyl ether. The resultant solid was isolated and washed with diethyl ether. The solid was then dissolved in methylene chloride and the solution was washed with a saturated aqueous sodium bicarbonate solution. The organic layer was washed in turn with water and brine, dried over magnesium sulphate and evaporated. There was thus obtained 4-chloro-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline (2.9 g);

10 NMR Spectrum: (DMSO_d₆) 1.3-1.5 (m, 2H), 1.75-1.9 (m, 4H), 2.0 (t, 1H), 2.25 (s, 3H), 2.85 (d, 2H), 4.02 (s, 3H), 4.12 (d, 2H), 7.41 (s, 1H), 7.46 (s, 1H), 8.9 (s, 1H).

[6] The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃COOD) 2.9 (s, 3H), 3.5-3.95 (br s, 14H), 4.05 (s, 3H), 4.4 (br s, 2H), 6.1 (s, 2H), 7.0 (m, 3H), 7.45 (s, 1H), 8.25 (s, 1H), 8.85 (s, 1H); Mass Spectrum: M+H⁺ 482.

15 The 4-chloro-6-methoxy-7-{2-[2-(4-methylpiperazin-1-yl)ethoxy]ethoxy}quinazoline used as a starting material was prepared as follows :-

Diiisopropyl azodicarboxylate (5.78 ml) was added dropwise to a stirred mixture of 7-hydroxy-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (6.0 g), 2-(2-chloroethoxy)ethanol (2.5 ml), triphenyl phosphine (7.7 g) and methylene chloride (150 ml) and the reaction mixture was stirred at ambient temperature for 2 hours. The solvent was evaporated and the residue was purified by column chromatography on silica using a 4:1 mixture of petroleum ether (b.p. 40-60°C) and ethyl acetate as eluent. There was thus obtained 7-[2-(2-chloroethoxy)ethoxy]-6-methoxy-3-pivaloyloxymethyl)-3,4-dihydroquinazolin-4-one (6.32 g); NMR Spectrum: (DMSO_d₆) 1.15 (s, 9H), 3.8 (m, 4H), 3.85 (m, 2H), 3.9 (s, 3H), 4.3 (m, 2H), 5.9 (s, 2H), 7.25 (s, 1H), 7.5 (s, 1H), 8.4 (s, 1H), Mass Spectrum: M+H⁺ 413.

A mixture of a portion (4.0 g) of the material so obtained and N-methylpiperazine (60 ml) was stirred and heated to 80°C for 5 hours. The mixture was evaporated and the residue partitioned between methylene chloride and a saturated aqueous ammonium chloride solution. The organic phase was dried over magnesium sulphate and evaporated. There was thus obtained 6-methoxy-7-{2-[2-(4-methylpiperazin-1-yl)ethoxy]ethoxy}-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (3.91 g); Mass Spectrum: M+H⁺ 477.

A mixture of the material so obtained, a 2N aqueous sodium hydroxide solution (7.95 ml) and methanol (20 ml) was stirred at ambient temperature for 2 hours. The basicity of the solution was adjusted to pH10 by the addition of 2N aqueous hydrochloric acid solution. The mixture was evaporated and the residue was triturated under methylene chloride. The resultant mixture was filtered and the filtrate was evaporated. The resultant residue was triturated under a mixture of diethyl ether and methanol. There was thus obtained 6-methoxy-7-{2-[2-(4-methylpiperazin-1-yl)ethoxy]ethoxy}-3,4-dihydroquinazolin-4-one (2.24 g); Mass Spectrum: M+H⁺ 363.

A mixture of the material so obtained, thionyl chloride (22 ml) and DMF (0.2 ml) was stirred and heated to 80°C for 1.5 hours. The mixture was evaporated, toluene was added and the mixture was again evaporated. Methylene chloride and water were added to the residue and the resultant mixture was cooled to 0°C and adjusted to pH12 by the successive addition of solid sodium bicarbonate and 2N aqueous sodium hydroxide solution. The organic phase was washed with brine, dried over magnesium sulphate and evaporated. The resultant yellow solid was triturated under a mixture of pentane and diethyl ether. There was thus obtained 4-chloro-6-methoxy-7-{2-[2-(4-methylpiperazin-1-yl)ethoxy]ethoxy}quinazoline (1.19 g); NMR Spectrum: (DMSO-d₆) 2.15 (s, 3H), 2.2-2.45 (br s, 8H), 2.5 (t, 2H), 3.6 (t, 2H), 3.85 (t, 2H), 4.05 (s, 3H), 4.4 (t, 2H), 7.45 (s, 1H), 7.5 (s, 1H), 8.9 (s, 1H), Mass Spectrum: M+H⁺ 381.

- 20 [7] 4-Chloro-6,7-dimethoxyquinazoline, used as a starting material, is described in European Patent Application No. 0566226 (Example 1 thereof). The product was obtained as a monohydrochloride salt and gave the following characterising data; NMR Spectrum: (DMSO-d₆) 4.0 (s, 6H), 6.05 (s, 2H), 6.95 (m, 3H), 7.35 (s, 1H), 8.2 (s, 1H), 8.8 (s, 1H); Mass Spectrum: M+H⁺ 326.
- 25 [8] Isopropanol was used in place of pentan-2-ol as the reaction solvent and the reaction mixture was heated to 80°C for 30 minutes. The product gave the following characterising data; NMR Spectrum: (DMSO-d₆ and CF₃CO₂D) 4.0 (s, 3H), 5.35 (s, 2H), 6.1 (s, 2H), 6.95 (m, 3H), 7.45 (m, 4H), 7.55 (d, 2H), 8.15 (s, 1H), 8.85 (s, 1H); Mass Spectrum: M+H⁺ 402.
- [9] The product gave the following characterising data; NMR Spectrum: (DMSO-d₆ and CF₃CO₂D) 2.35 (m, 2H), 3.15 (m, 2H), 3.35 (m, 2H), 3.55 (d, 2H), 3.8 (m, 2H), 4.0 (m, 2H), 4.05 (s, 3H), 4.35 (m, 2H), 6.15 (s, 2H), 7.05 (d, 1H), 7.15 (d, 1H), 7.45 (s, 1H), 8.25 (s, 1H), 8.9 (s, 1H); Mass Spectrum: M-H⁻ 455 and 457.

The 6-chloro-2,3-methylenedioxylaniline used as a starting material was prepared as follows :-

Sulphuryl chloride (72.5 ml) was added dropwise during 1.7 hours to a stirred mixture of benzodioxole (100 g), aluminium trichloride (0.43 g) and diphenyl sulphide (0.55 ml).

- 5 Once the reaction started with the evolution of sulphur dioxide, the reaction mixture was cooled in a water bath to a temperature of approximately 22°C. After completion of the addition, the reaction mixture was stirred at ambient temperature for 45 minutes. The reaction mixture was degassed under vacuum and filtered and the filtrate was distilled at atmospheric pressure using a Vigreux distillation column. There was thus obtained 5-chloro-
- 10 1,3-benzodioxole; b.p. 185-187°C; NMR Spectrum: (CDCl₃) 6.0 (s, 2H); 6.7 (d, 1H); 6.75-6.9 (m, 2H).

A mixture of diisopropylamine (4.92 ml) and THF (100 ml) was cooled to -78°C and n-butyllithium (2.5 M in hexane, 14 ml) was added dropwise. The mixture was stirred at -78°C for 15 minutes. 5-Chloro-1,3-benzodioxole (3.73 ml) was added dropwise and the 15 reaction mixture was stirred at -78°C for 30 minutes. Dry carbon dioxide gas was bubbled into the reaction mixture for 30 minutes. The resultant reaction mixture was allowed to warm to ambient temperature and was stirred for a further hour. Water was added and the organic solvent was evaporated. The residue was acidified to pH2 by the addition of 2N aqueous hydrochloric acid solution. The resultant solid was isolated and washed in turn with water and 20 diethyl ether. There was thus obtained 5-chloro-1,3-benzodioxole-4-carboxylic acid (5.4 g); NMR Spectrum: (DMSO-d₆) 6.15 (s, 2H), 7.0 (m, 2H), 13.7 (br s, 1H).

A portion (1g) of the material so obtained was dissolved in 1,4-dioxane (15 ml) and anhydrous tert-butanol (4 ml), diphenylphosphoryl azide (1.12 ml) and triethylamine (0.73 ml) were added in turn. The resultant mixture was stirred and heated to 100°C for 4 hours. The 25 mixture was evaporated and the residue was partitioned between ethyl acetate and a 5% aqueous citric acid solution. The organic phase was washed in turn with water, a saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 9:1 mixture of petroleum ether (b.p. 40-60°C) and ethyl acetate as eluent. There was thus obtained 30 tert-butyl 5-chloro-1,3-benzodioxol-4-ylcarbamate (1.1 g); NMR Spectrum: (DMSO-d₆) 1.45 (s, 9H), 6.1 (s, 2H), 6.85 (d, 1H), 6.95 (d, 1H), 8.75 (s, 1H).

A mixture of the material so obtained (1.1 g), trifluoroacetic acid (6 ml) and methylene chloride (20 ml) was stirred at ambient temperature for 3 hours. The solvent was evaporated

and the residue was partitioned between ethyl acetate and a saturated aqueous sodium bicarbonate solution. The organic phase was washed with brine, dried over magnesium sulphate and evaporated. There was thus obtained 6-chloro-2,3-methylenedioxylaniline (0.642 g); NMR Spectrum: (DMSO_d₆) 5.15 (s, 2H), 6.0 (s, 2H), 6.25 (d, 1H), 6.75 (d, 1H).

5 [10] The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 2.35 (m, 2H), 3.15 (m, 2H), 3.35 (m, 2H), 3.5 (m, 2H), 3.8 (m, 2H), 4.0 (m, 2H), 4.05 (s, 3H), 4.35 (m, 2H), 6.15 (s, 2H), 7.05 (d, 1H), 7.15 (d, 1H), 7.45 (s, 1H), 8.25 (s, 1H), 8.9 (s, 1H); Mass Spectrum: M+H⁺ 473 and 475.

[11] The reaction product was purified by column chromatography on silica using a 4:1 mixture of methylene chloride and methanol as eluent. The material so obtained was dissolved in a mixture of methylene chloride and methanol and a 6M solution of hydrogen chloride in diethyl ether was added. The dihydrochloride salt so obtained was isolated and dried and gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 2.65 (m, 2H), 2.9 (s, 3H), 3.35-3.55 (br m, 6H), 3.7-3.9 (br m, 4H), 4.05 (s, 3H), 4.35 (m, 2H), 15 6.15 (s, 2H), 7.05 (d, 1H), 7.15 (d, 1H), 7.45 (s, 1H), 8.25 (s, 1H), 8.85 (s, 1H); Mass Spectrum: M+H⁺ 486 and 488.

[12] The reaction product was purified by column chromatography on silica using a 9:8:2 mixture of methylene chloride, methanol and a saturated methanolic ammonia solution as eluent. The material so obtained was dissolved in a mixture of methylene chloride and methanol and a 6M solution of hydrogen chloride in diethyl ether was added. The dihydrochloride salt so obtained was isolated and gave the following characterising data; NMR Spectrum: (DMSO_d₆ and K₂CO₃) 1.55 (m, 2H), 1.9 (m, 2H), 2.0 (m, 1H), 2.5 (m, 5H), 3.15 (m, 2H), 3.95 (s, 3H), 4.05 (m, 2H), 6.1 (s, 2H), 6.95 (d, 1H), 7.05 (d, 1H), 7.2 (s, 1H), 7.9 (s, 1H), 8.35 (d, 1H), 9.55 (s, 1H); Mass Spectrum: M-H⁻ 455 and 457.

25 [13] The following variation of the standard reaction procedure was used :-
A mixture of 7-benzyloxy-4-chloro-6-methoxyquinazoline (3 g), 5-chloro-2,3-methylenedioxylaniline (1.88 g), a 6M solution of hydrogen chloride in isopropanol (0.166 ml) and isopropanol (60 ml) was stirred and heated to 80°C for 3 hours. The reaction mixture was allowed to cooled to ambient temperature and the solid was isolated, washed with 30 isopropanol and with diethyl ether. There was thus obtained the required product as a dihydrochloride salt (4.18 g); NMR Spectrum: (DMSO_d₆) 4.0 (s, 3H), 5.35 (s, 2H), 6.15 (s, 2H), 7.05 (d, 1H), 7.15 (d, 1H), 7.45 (m, 4H), 7.55 (d, 2H), 8.25 (s, 1H), 8.8 (s, 1H).

[14] The reaction product was purified by column chromatography on silica using increasingly polar mixture of methylene chloride and a saturated methanolic ammonia solution as eluent. The product was obtained as the free base and gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 2.3 (m, 2H), 3.15 (m, 2H), 3.35 (t, 2H), 3.55 5 (d, 2H), 3.7 (t, 2H), 4.0 (s, 3H), 4.05 (m, 2H), 4.35 (t, 2H), 6.15 (s, 2H), 7.05 (d, 1H), 7.3 (d, 1H), 7.4 (s, 1H), 8.15 (s, 1H), 8.9 (s, 1H); Mass Spectrum: M+H⁺ 517 and 519.

The 6-bromo-2,3-methylenedioxylaniline used as a starting material was prepared from 5-bromo-1,3-benzodioxole (Aldrich Chemical Company) using analogous procedures to those described in Note [9] above for the preparation of 6-chloro-2,3-methylenedioxylaniline. There 10 were thus obtained in turn :-

5-bromo-1,3-benzodioxole-4-carboxylic acid; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 6.15 (s, 2H), 6.95 (d, 1H), 7.1 (d, 1H); Mass Spectrum: [M-H]⁻ 243; tert-butyl 5-bromo-1,3-benzodioxol-4-ylcarbamate; NMR Spectrum: (DMSO_d₆) 1.45 (s, 9H), 6.1 (s, 2H), 6.80 (d, 1H), 7.1 (d, 1H), 8.70 (s, 1H); and 15 6-bromo-2,3-methylenedioxylaniline; NMR Spectrum: (DMSO_d₆) 5.05 (s, 2H), 6.0 (s, 2H), 6.25 (d, 1H), 6.9 (d, 1H); Mass Spectrum: M+H⁺ 216 and 218.

[15] The reaction product was purified by column chromatography on silica using increasingly polar mixture of methylene chloride and a saturated methanolic ammonia solution as eluent. The product was obtained as the free base and gave the following 20 characterising data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 2.3 (m, 2H), 3.05 (s, 3H), 3.35 (t, 2H), 4.05 (s, 3H), 4.35 (t, 2H), 6.15 (s, 2H), 7.05 (d, 1H), 7.3 (d, 1H), 7.35 (s, 1H), 8.15 (s, 1H), 8.9 (s, 1H); Mass Spectrum: M+H⁺ 510 and 512; Elemental Analysis: Found C, 47.44; H, 4.24; N, 7.92; C₂₀H₂₀BrN₃O₆S requires C, 47.07; H, 3.95; N, 8.23%.

The 4-chloro-6-methoxy-7-(3-methylsulphonylpropoxy)quinazoline used as a starting 25 material is described in International Patent Application WO 00/47212 (example 50 thereof).

[16] The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 2.35 (m, 2H), 3.15 (m, 2H), 3.35 (m, 2H), 3.55 (m, 2H), 3.75 (s, 3H), 3.8 (m, 2H), 4.0 (br s, 5H), 4.35 (m, 2H), 6.05 (s, 2H), 6.55 (s, 1H), 6.75 (s, 1H), 7.4 (s, 1H), 8.2 (s, 1H), 8.9 (s, 1H); Mass Spectrum: M+H⁺ 469; Elemental Analysis: Found C, 51.59; H, 6.01; 30 N, 9.46; C₂₄H₂₈N₄O₆ 2.1HCl 0.8H₂O requires C, 51.52; H, 5.71; N, 10.01%.

The 5-methoxy-2,3-methylenedioxylaniline used as a starting material was prepared from 4-bromo-6-methoxy-1,3-benzodioxole (J Org. Chem., 1985, 50, 5077) using analogous

procedures to those described in Note [9] above for the preparation of 6-chloro-2,3-methylenedioxyaniline. There were thus obtained in turn :-

6-methoxy-1,3-benzodioxole-4-carboxylic acid; NMR Spectrum: (DMSO_d₆) 3.75 (s, 3H), 6.1 (s, 2H), 6.7 (s, 1H), 6.85 (s, 1H), 13.0 (br s, 1H);

5 tert-butyl 6-methoxy-1,3-benzodioxol-4-ylcarbamate; NMR Spectrum: (DMSO_d₆) 1.45 (s, 9H), 3.7 (s, 3H), 5.95 (s, 2H), 6.4 (s, 1H), 6.55 (br s, 1H), 8.85 (br s, 1H); Mass Spectrum: M+Na⁺ 290; and

5-methoxy-2,3-methylenedioxyaniline; NMR Spectrum: (DMSO_d₆) 3.6 (s, 3H), 4.95 (br s, 2H), 5.85 (s, 2H), 5.9 (s, 1H); Mass Spectrum: M+H⁺ 168.

10 [17] The product gave the following characterising data; Mass Spectrum: M+H⁺ 497.

The 7-(2-acetoxy-3-morpholinopropoxy)-4-chloro-6-methoxyquinazoline used as a starting material was prepared as follows :-

A mixture of 7-hydroxy-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (40 g), 2,3-epoxypropyl bromide (16.8 ml), potassium carbonate (36 g) and DMF (400 ml)

15 was stirred and heated to 70°C for 1.5 hours. The mixture was poured into an ice-water mixture (1.5 L) and the resultant precipitate was isolated, washed in turn with water and diethyl ether and dried under vacuum over phosphorus pentoxide. There was thus obtained 7-(2,3-epoxypropoxy)-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (46.7 g).

A mixture of a portion (8 g) of the material so obtained, morpholine (5.8 ml) and 20 chloroform (120 ml) was heated to reflux for 16 hours. The mixture was evaporated and the residue was purified by column chromatography on silica using a 19:1 mixture of methylene chloride and methanol as eluent. There was thus obtained 7-(2-hydroxy-3-morpholinopropoxy)-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one as a foam (8.2 g); NMR Spectrum: (CDCl₃) 1.2 (s, 9H), 2.5 (m, 2H), 2.6 (m, 2H), 2.7 (m, 2H), 3.5 (br s, 1H), 3.75 (m, 4H), 3.95 (s, 3H), 4.15 (m, 2H), 4.25 (m, 1H), 5.95 (s, 2H), 7.15 (s, 1H), 7.65 (s, 1H), 8.2 (s, 1H).

A mixture of the material so obtained and a saturated methanolic ammonia solution was stirred at ambient temperature for 24 hours. The mixture was evaporated and the resultant solid was washed with diethyl ether and a 19:1 mixture of diethyl ether and methylene 30 chloride. There was thus obtained 7-(2-hydroxy-3-morpholinopropoxy)-6-methoxy-3,4-dihydroquinazolin-4-one (6.34 g); NMR Spectrum: (DMSO_d₆) 2.4 (m, 6H), 3.55 (m, 4H), 3.85 (s, 3H), 4.0 (m, 2H), 4.15 (m, 1H), 4.95 (br s, 1H), 7.15 (s, 1H), 7.45 (s, 1H), 7.95 (s, 1H).

A mixture of a portion (5.2 g) of the material so obtained, acetic anhydride (20 ml) and pyridine (1 ml) was stirred at ambient temperature for 30 minutes. The resultant mixture was poured into an ice-water mixture and stirred for 30 minutes. The mixture was then cooled in an ice-bath and a saturated solution of sodium bicarbonate was slowly added to adjust the pH 5 to 9. The mixture was extracted with methylene chloride and the organic phase was washed with water and with brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 93:7 mixture of methylene chloride and methanol as eluent. There was thus obtained 7-(2-acetoxy-3-morpholinopropoxy)-6-methoxy-
10 3,4-dihydroquinazolin-4-one as a solid (5 g); NMR Spectrum: (DMSO_d₆) 2.05 (s, 3H), 2.4 (m, 1H), 2.6 (m, 2H), 3.55 (m, 4H), 3.85 (s, 3H), 4.35 (m, 2H), 5.25 (m, 1H), 7.2 (s, 1H), 7.45 (s, 1H), 8.0 (s, 1H); Mass Spectrum: M+H⁺ 378.

A mixture of the material so obtained, thionyl chloride (60 ml) and DMF (0.5 ml) was heated to reflux for 1 hour. The mixture was evaporated, toluene was added and the mixture was evaporated. A mixture of ice and water was added to the residue and the mixture was
15 basified to pH8.5 by the addition of a saturated aqueous sodium bicarbonate solution. The mixture was extracted with methylene chloride. The organic phase was washed with water and with brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 97:3 mixture of methylene chloride and methanol as eluent. There was thus obtained 7-(2-acetoxy-3-morpholinopropoxy)-4-chloro-
20 6-methoxyquinazoline as a foam (4.56 g); NMR Spectrum: (CDCl₃) 2.1 (s, 3H), 2.55 (m, 4H), 2.7 (d, 2H), 3.7 (m, 4H), 4.05 (s, 3H), 4.35 (m, 1H), 4.45 (m, 1H), 5.45 (m, 1H), 7.4 (d, 2H), 8.85 (s, 1H); Mass Spectrum: M+H⁺ 396 and 398.

[18] The product gave the following characterising data; Mass Spectrum: M+H⁺ 481.

The 7-(2-acetoxy-3-pyrrolidin-1-ylpropoxy)-4-chloro-6-methoxyquinazoline used as a
25 starting material was prepared as follows :-

7-(2,3-Epoxypropoxy)-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one was reacted with pyrrolidine using an analogous procedure to that described in the second paragraph of the portion of Note [17] immediately above that is concerned with the preparation of starting materials. There was thus obtained 7-(2-hydroxy-
30 3-pyrrolidin-1-ylpropoxy)-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one.

The material so obtained was taken through an analogous sequence of reactions to those described in the third to fifth paragraphs of the portion of Note [17] immediately above that is concerned with the preparation of starting materials. There was thus obtained

7-(2-acetoxy-3-pyrrolidin-1-ylpropoxy)-4-chloro-6-methoxyquinazoline; NMR Spectrum: (CDCl₃ and CD₃CO₂D) 2.05 (s, 4H), 2.15 (s, 3H), 3.45 (br s, 4H), 3.65 (m, 2H), 4.05 (s, 3H), 4.4 (d, 2H), 5.65 (m, 1H), 7.4 (s, 1H), 7.55 (s, 1H), 8.9 (s, 1H).

[19] The product gave the following characterising data; Mass Spectrum: M+H⁺ 495.

5 The 7-(2-acetoxy-3-piperidinopropoxy)-4-chloro-6-methoxyquinazoline used as a starting material was prepared as follows :-

7-(2,3-Epoxypropoxy)-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one was reacted with piperidine using an analogous procedure to that described in the second paragraph of the portion of Note [17] immediately above that is concerned with the preparation of starting materials. There was thus obtained 7-(2-hydroxy-3-piperidinopropoxy)-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one.

The material so obtained was taken through an analogous sequence of reactions to those described in the third to fifth paragraphs of the portion of Note [17] immediately above that is concerned with the preparation of starting materials. There was thus obtained

15 7-(2-acetoxy-3-piperidinopropoxy)-4-chloro-6-methoxyquinazoline; NMR Spectrum: (CDCl₃ and CD₃CO₂D) 1.6 (m, 2H), 1.9 (m, 4H), 2.1 (s, 3H), 3.2 (br s, 4H), 3.5 (m, 2H), 4.05 (s, 3H), 4.35 (m, 2H), 5.7 (m, 1H), 7.4 (s, 1H), 7.5 (s, 1H), 8.9 (s, 1H).

[20] The product gave the following characterising data; Mass Spectrum: M+H⁺ 535.

The 7-[2-acetoxy-3-(4-cyanomethylpiperazin-1-yl)propoxy]-4-chloro-6-methoxyquinazoline used as a starting material was prepared as follows :-

7-(2,3-Epoxypropoxy)-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one was reacted with 1-cyanomethylpiperazine using an analogous procedure to that described in the second paragraph of the portion of Note [17] immediately above that is concerned with the preparation of starting materials. There was thus obtained 7-[3-(4-cyanomethylpiperazin-1-yl)-2-hydroxypropoxy]-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one.

The material so obtained was taken through an analogous sequence of reactions to those described in the third to fifth paragraphs of the portion of Note [17] immediately above that is concerned with the preparation of starting materials. There was thus obtained

7-[2-acetoxy-3-(4-cyanomethylpiperazin-1-yl)propoxy]-4-chloro-6-methoxyquinazoline;

30 NMR Spectrum: (CDCl₃) 2.1 (s, 3H), 2.65 (br s, 10H), 3.5 (s, 2H), 4.05 (s, 3H), 4.4 (m, 2H), 5.45 (m, 1H), 7.25 (s, 1H), 7.4 (s, 1H), 8.85 (s, 1H); Mass Spectrum: M+H⁺ 434 and 436.

The 1-cyanomethylpiperazine used as a starting material was prepared as follows :-

A mixture of 1-(*tert*-butoxycarbonyl)piperazine (5 g), 2-chloroacetonitrile (1.9 ml), potassium carbonate (4 g) and DMF (20 ml) was stirred at ambient temperature for 16 hours. A saturated aqueous ammonium chloride solution was added and the mixture was extracted with ethyl acetate. The organic phase was dried over magnesium sulphate and evaporated.

- 5 The residue was purified by column chromatography on silica using diethyl ether as eluent. There was thus obtained 1-(*tert*-butoxycarbonyl)-4-cyanomethylpiperazine as a solid (5.7 g); NMR Spectrum: (CDCl₃) 1.45 (s, 9H), 2.5 (m, 4H), 3.45 (m, 4H), 3.55 (s, 2H).

A mixture of the material so obtained, trifluoroacetic acid (20 ml) and methylene chloride (25 ml) was stirred at ambient temperature for 4 hours. The mixture was evaporated, 10 toluene was added and the mixture was evaporated again. The residue was purified by column chromatography on silica using a 9:1 mixture of methylene chloride and methanol as eluent. There was thus obtained 1-cyanomethylpiperazine trifluoroacetate salt which was treated with solid sodium bicarbonate in a mixture of methylene chloride, ethyl acetate and methanol to give the free base form (2.9 g); NMR Spectrum: (CDCl₃ and DMSO_d₆) 2.7 (m, 15 4H), 3.2 (m, 4H), 3.6 (s, 2H), 6.2 (br s, 1H).

- [21] The product gave the following characterising data; Mass Spectrum: M+H⁺ 483.

The 7-[2-acetoxy-3-(*N*-isopropyl-*N*-methylamino)propoxy]-4-chloro-6-methoxyquinazoline used as a starting material was prepared as follows :-

7-(2,3-Epoxypropoxy)-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one 20 was reacted with *N*-isopropyl-*N*-methylamine using an analogous procedure to that described in the second paragraph of the portion of Note [17] immediately above that is concerned with the preparation of starting materials. There was thus obtained 7-[2-hydroxy-3-(*N*-isopropyl-*N*-methylamino)propoxy]-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one.

The material so obtained was taken through an analogous sequence of reactions to 25 those described in the third to fifth paragraphs of the portion of Note [17] immediately above that is concerned with the preparation of starting materials. There was thus obtained 7-[2-acetoxy-3-(*N*-isopropyl-*N*-methylamino)propoxy]-4-chloro-6-methoxyquinazoline; NMR Spectrum: (CDCl₃) 1.0 (d, 6H), 2.1 (s, 3H), 2.3 (s, 3H), 2.6 (m, 1H), 2.75 (m, 1H), 2.85 (m, 1H), 4.05 (s, 3H), 4.35 (m, 1H), 4.45 (m, 1H), 5.35 (m, 1H), 7.25 (s, 1H), 7.4 (s, 1H), 8.85 (s, 30 1H).

- [22] The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 1.3 (m, 2H), 1.7 (m, 2H), 1.9-2.2 (m, 4H), 2.8 (s, 3H), 3.05 (m, 2H), 3.5 (m, 2H),

3.75 (s, 3H), 4.05 (s, 3H), 4.1 (m, 2H), 6.05 (s, 2H), 6.55 (s, 1H), 6.7 (s, 1H), 7.45 (s, 1H), 8.2 (s, 1H), 8.85 (s, 1H).

[23] Isopropanol was used in place of pentan-2-ol as the reaction solvent and the reaction mixture was heated to 80°C for 1.5 hours. The reaction mixture was cooled to ambient 5 temperature and evaporated. A mixture of the residue and methylene chloride (5 ml) was diluted with 1N aqueous sodium hydroxide solution (2 ml) and extracted with methylene chloride. The organic phase was evaporated and the residue was purified by column chromatography on silica using a 9:10:1 mixture of methylene chloride, ethyl acetate and a saturated methanolic ammonia solution as eluent. The material so obtained was dissolved in 10 diethyl ether and a 6M solution of hydrogen chloride in isopropanol was added. The dihydrochloride salt so obtained was isolated and dried and gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 1.4-1.5 (m, 2H), 1.7-1.9 (m, 3H), 2.0 (d, 2H), 2.75 (s, 3H), 2.95 (m, 2H), 3.45 (d, 2H), 4.0 (s, 3H), 4.3 (t, 2H), 6.1 (s, 2H), 7.0 (m, 3H), 7.38 (s, 1H), 8.12 (s, 1H), 8.9 (s, 1H); Mass Spectrum: M+H⁺ 437.

15 The 4-chloro-6-methoxy-7-[2-(N-methylpiperidin-4-yl)ethoxy]quinazoline used as a starting material is described International Patent Application WO 00/47212 (within Example 241 thereof).

[24] 7-(N-tert-Butoxycarbonylpiperidin-4-ylmethoxy)-4-chloro-6-methoxyquinazoline was used as the appropriate 4-chloroquinazoline, isopropanol was used in place of pentan-2-ol as 20 the reaction solvent, a 6M solution of hydrogen chloride in isopropanol (0.02 ml) was added and the reaction mixture was heated to 80°C for 1 hour. The product was obtained as the monohydrochloride salt and gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 1.5-1.65 (m, 2H), 2.0 (d, 2H), 2.15-2.3 (m, 1H), 2.95 (m, 2H), 3.3-3.4 (m, 2H), 4.02 (s, 3H), 4.1 (d, 2H), 6.07 (s, 2H), 7.0 (s, 3H), 7.4 (s, 1H), 8.25 (s, 1H), 8.65 (m, 1H), 8.8 (s, 1H), 8.95 (m, 1H); Mass Spectrum: M+H⁺ 409.

The 7-(N-tert-butoxycarbonylpiperidin-4-ylmethoxy)-4-chloro-6-methoxyquinazoline used as a starting material was prepared as follows :-

Sodium hydride (60% suspension in mineral oil, 1.44 g) was added portionwise during 20 minutes to a solution of 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one 30 (International Patent Application WO 97/22596, Example 1 thereof; 8.46 g) in DMF (70 ml). The mixture was stirred at ambient temperature for 1.5 hours. Chloromethyl pivalate (5.65 g) was added dropwise and the mixture was stirred at ambient temperature for 2 hours. The mixture was diluted with ethyl acetate (100 ml) and poured onto a mixture (400 ml) of ice and

water containing 2N aqueous hydrochloric acid (4 ml). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined extracts were washed with brine, dried over magnesium sulphate and evaporated. The residue was triturated under a mixture of diethyl ether and petroleum ether (b.p. 60-80°C) and the resultant solid was 5 collected and dried under vacuum. There was thus obtained 7-benzyloxy-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (10 g); NMR Spectrum: (DMSO_d₆) 1.11 (s, 9H), 3.89 (s, 3H), 5.3 (s, 2H), 5.9 (s, 2H), 7.27 (s, 1H), 7.35 (m, 1H), 7.47 (t, 2H), 7.49 (d, 2H), 7.51 (s, 1H), 8.34 (s, 1H).

A mixture of a portion (7 g) of the material so obtained, 10% palladium-on-charcoal 10 catalyst (0.7 g), DMF (50 ml), methanol (50 ml), acetic acid (0.7 ml) and ethyl acetate (250 ml) was stirred under an atmosphere pressure of hydrogen for 40 minutes. The catalyst was removed by filtration and the solvent was evaporated. The residue was triturated under diethyl ether and the resultant solid was collected and dried under vacuum. There was thus obtained 7-hydroxy-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (4.36 g); 15 NMR Spectrum: (DMSO_d₆) 1.1 (s, 9H), 3.89 (s, 3H), 5.89 (s, 2H), 7.0 (s, 1H), 7.48 (s, 1H), 8.5 (s, 1H).

A mixture of 7-hydroxy-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (4 g), N-tert-butoxycarbonyl-4-(4-toluenesulphonyloxymethyl)piperidine (10 g), potassium carbonate (7 g) in DMF (50 ml) and the resultant mixture was stirred and heated to 95°C for 20 2.5 hours. The mixture was cooled to ambient temperature and partitioned between water and a mixture of ethyl acetate and diethyl ether. The organic layer was washed in turn with water and brine, dried over magnesium sulphate and evaporated. The resulting oil was crystallised from petroleum ether (b.p. 60-80°C) and the suspension was stored overnight at 5°C. The resultant solid was collected by filtration, washed with petroleum ether and dried under 25 vacuum. There was thus obtained 7-(N-tert-butoxycarbonylpiperidin-4-ylmethoxy)-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one which was used without further purification.

A mixture of 7-(N-tert-butoxycarbonylpiperidin-4-ylmethoxy)-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (6 g) and a saturated methanolic ammonia 30 solution (100ml) was stirred at ambient temperature for 16 hours. The resultant mixture was evaporated and the residue was triturated under diethyl ether. The solid so obtained was isolated, washed with a 49:1 mixture of diethyl ether and methylene chloride and dried under vacuum. There was thus obtained 7-(N-tert-butoxycarbonylpiperidin-4-ylmethoxy)-

6-methoxy-3,4-dihydroquinazolin-4-one (3.3 g); NMR Spectrum: (DMSO_d₆) 1.12-1.3 (m, 2H), 1.42 (s, 9H), 1.8 (d, 2H), 2.02 (m, 1H), 2.7-2.9 (m, 2H), 3.9 (s, 3H), 4.02 (m, 4H), 7.15 (s, 1H), 7.45 (s, 1H), 8.0 (s, 1H).

A mixture of a portion (0.2 g) of the material so obtained, carbon tetrachloride (0.15 ml), triphenylphosphine (0.25 g) and 1,2-dichloroethane (10 ml) was stirred and heated to 70°C for 2 hours. The mixture was evaporated and the residue was purified by column chromatography on silica using a 5:4:1 mixture of methylene chloride, ethyl acetate and methanol as eluent. There was thus obtained 7-(N-tert-butoxycarbonylpiperidin-4-ylmethoxy)-4-chloro-6-methoxyquinazoline (0.07 g); NMR Spectrum: (DMSO_d₆) 1.15-1.3 (m, 2H), 1.45 (s, 9H), 1.8 (d, 2H), 2.08 (m, 1H), 2.7-2.9 (m, 2H), 4.02 (m, 5H), 4.12 (d, 2H), 7.42 (s, 1H), 7.5 (s, 1H), 8.9 (s, 1H); Mass Spectrum: M+H⁺ 408.

The N-tert-butoxycarbonyl-4-(4-toluenesulphonyloxymethyl)piperidine used as a starting material was prepared as follows :-

A solution of di-tert-butyl dicarbonate (41.7 g) in ethyl acetate (75 ml) was added dropwise to a stirred solution of ethyl piperidine-4-carboxylate (30 g) in ethyl acetate (150 ml) which had been cooled to 0 to 5°C in an ice-bath. The resultant mixture was stirred at ambient temperature for 48 hours. The mixture was poured into water (300 ml). The organic layer was separated, washed in turn with water (200 ml), 0.1N aqueous hydrochloric acid solution (200 ml), a saturated aqueous sodium bicarbonate solution (200 ml) and brine (200 ml), dried over magnesium sulphate and evaporated. There was thus obtained ethyl N-tert-butoxycarbonylpiperidine-4-carboxylate (48 g); NMR Spectrum: (CDCl₃) 1.25 (t, 3H), 1.45 (s, 9H), 1.55-1.7 (m, 2H), 1.8-2.0 (d, 2H), 2.35-2.5 (m, 1H), 2.7-2.95 (t, 2H), 3.9-4.1 (br s, 2H), 4.15 (q, 2H).

A solution of the material so obtained in THF (180 ml) was cooled at 0°C and lithium aluminium hydride (1M solution in THF; 133 ml) was added dropwise. The mixture was stirred at 0°C for 2 hours. Water (30 ml) and 2N aqueous sodium hydroxide solution (10 ml) were added in turn and the mixture was stirred for 15 minutes. The resultant mixture was filtered through diatomaceous earth and the solids were washed with ethyl acetate. The filtrate was washed in turn with water and with brine, dried over magnesium sulphate and evaporated. There was thus obtained N-tert-butoxycarbonyl-4-hydroxymethylpiperidine (36.3 g); NMR Spectrum: (CDCl₃) 1.05-1.2 (m, 2H), 1.35-1.55 (m, 10H), 1.6-1.8 (m, 2H), 2.6-2.8 (t, 2H), 3.4-3.6 (t, 2H), 4.0-4.2 (br s, 2H).

- 1,4-Diazabicyclo[2.2.2]octane (42.4 g) was added to a solution of N-tert-butoxycarbonyl-4-hydroxymethylpiperidine (52.5 g) in tert-butyl methyl ether (525 ml) and the mixture was stirred at ambient temperature for 15 minutes. The mixture was then cooled in an ice-bath to 5°C and a solution of 4-toluenesulphonyl chloride (62.8 g) in 5 tert-butyl methyl ether (525 ml) was added dropwise over 2 hours while maintaining the reaction temperature at approximately 0°C. The resultant mixture was allowed to warm to ambient temperature and was stirred for 1 hour. Petroleum ether (b.p. 60-80°C, 1L) was added and the precipitate was removed by filtration. The filtrate was evaporated to give a solid residue which was dissolved in diethyl ether. The organic solution was washed in turn 10 with 0.5N aqueous hydrochloric acid solution, water, a saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulphate and evaporated. There was thus obtained N-tert-butoxycarbonyl-4-(4-toluenesulphonyloxymethyl)piperidine (76.7 g); NMR Spectrum: (CDCl₃) 1.0-1.2 (m, 2H), 1.45 (s, 9H), 1.65 (d, 2H), 1.75-1.9 (m, 2H), 2.45 (s, 3H), 2.55-2.75 (m, 2H), 3.85 (d, 1H), 4.0-4.2 (br s, 2H), 7.35 (d, 2H), 7.8 (d, 2H).
- 15 [25] 7-[2-(N-tert-Butoxycarbonylpiperidin-4-yl)ethoxy]-4-chloro-6-methoxyquinazoline was used as the appropriate 4-chloroquinazoline, isopropanol was used in place of pentan-2-ol as the reaction solvent, a 6M solution of hydrogen chloride in isopropanol (0.02 ml) was added and the reaction mixture was heated to 80°C for 1 hour. The product was obtained as the monohydrochloride salt and gave the following characterising data; NMR Spectrum:
- 20 (DMSO_d₆ and CF₃CO₂D) 1.4-1.55 (m, 2H), 1.9 (br s, 2H), 1.95 (d, 2H), 2.95 (m, 2H), 3.4 (d, 2H), 4.1 (s, 3H), 4.35 (m, 2H), 6.15 (s, 2H), 7.0 (s, 3H), 7.4 (s, 1H), 8.15 (s, 1H), 8.9 (s, 1H); Mass Spectrum: M+H⁺ 423.

The 7-[2-(N-tert-butoxycarbonylpiperidin-4-yl)ethoxy]-4-chloro-6-methoxyquinazoline used as a starting material was obtained as follows :-

- 25 A mixture of 7-hydroxy-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (2 g), N-tert-butoxycarbonyl-4-[2-(4-toluenesulphonyloxy)ethyl]piperidine (2.84 g), potassium carbonate (1.8 g) and DMF (20 ml) was stirred and heated to 95°C for 2.5 hours. The resultant mixture was cooled to ambient temperature and poured onto a mixture of ice and water. The mixture was extracted with methylene chloride. The organic layer was washed 30 with brine, dried over magnesium sulphate and evaporated. There was thus obtained 7-[2-(N-tert-butoxycarbonylpiperidin-4-yl)ethoxy]-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (2 g); NMR Spectrum: (DMSO_d₆) 1.0-1.15 (m, 2H), 1.15 (s,

9H), 1.4 (s, 9H), 1.6-1.8 (m, 3H), 2.6-2.8 (m, 2H), 3.92 (s, 3H), 3.9-4.0 (m, 2H), 4.2 (m, 2H), 5.92 (s, 2H), 7.2 (s, 1H), 7.5 (s, 1H), 8.3 (s, 1H).

A mixture of 7-[2-(N-tert-butoxycarbonylpiperidin-4-yl)ethoxy]-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (2 g) and a saturated methanolic ammonia solution (30ml) was stirred at ambient temperature for 16 hours. The resultant mixture was evaporated and the residue was triturated under diethyl ether. The solid so obtained was isolated, washed with a 49:1 mixture of diethyl ether and methylene chloride and dried under vacuum. There was thus obtained 7-[2-(N-tert-butoxycarbonylpiperidin-4-yl)ethoxy]-6-methoxy-3,4-dihydroquinazolin-4-one (1.3 g); NMR Spectrum: (DMSO_d₆) 1.0-1.15 (m, 2H), 1.4 (s, 9H), 1.6-1.8 (m, 3H), 2.6-2.8 (m, 2H), 3.3-3.5 (m, 2H), 3.9 (s, 3H), 3.9-4.0 (m, 2H), 4.18 (m, 2H), 7.15 (s, 1H), 7.45 (s, 1H), 8.0 (s, 1H); Mass Spectrum: M+H⁺ 404.

Using an analogous procedure to that described in the last paragraph of the portion of Note [24] immediately above that is concerned with the preparation of 7-(N-tert-butoxycarbonylpiperidin-4-ylmethoxy)-4-chloro-6-methoxyquinazoline, 15 7-[2-(N-tert-butoxycarbonylpiperidin-4-yl)ethoxy]-6-methoxy-3,4-dihydroquinazolin-4-one (0.2 g) was reacted with carbon tetrachloride and triphenylphosphine to give 7-[2-(N-tert-butoxycarbonylpiperidin-4-yl)ethoxy]-4-chloro-6-methoxyquinazoline (0.03 g); NMR Spectrum: (DMSO_d₆) 1.0-1.2 (m, 2H), 1.4 (s, 9H), 1.6-1.8 (m, 5H), 2.6-2.8 (m, 2H), 3.92 (d, 2H), 4.0 (s, 3H), 4.3 (m, 2H), 7.4 (s, 1H), 7.5 (s, 1H), 8.9 (s, 1H).

20 The N-tert-butoxycarbonyl-4-[2-(4-toluenesulphonyloxy)ethyl]piperidine used as a starting material was prepared by the reaction of 4-toluenesulphonyl chloride with N-tert-butoxycarbonyl-4-(2-hydroxyethyl)piperidine (International Patent Application WO 00/47212, in example 126 thereof) using an analogous procedure to that described in the last paragraph of the portion of Note [24] immediately above that is concerned with the 25 preparation of N-tert-butoxycarbonyl-4-(4-toluenesulphonyloxy)methyl)piperidine.

[26] Isopropanol was used in place of pentan-2-ol as the reaction solvent, a 6M solution of hydrogen chloride in isopropanol was added and the reaction mixture was heated to 80°C for 3 hours. The reaction mixture was evaporated and the residue was purified by column chromatography on silica using increasingly polar mixture of methylene chloride and a 30 saturated methanolic ammonia solution as eluent. The material so obtained was dissolved in diethyl ether and a 3M solution of hydrogen chloride in diethyl ether was added. The precipitate was isolated and dried. The resultant product was obtained as the monohydrochloride salt and gave the following characterising data; NMR Spectrum:

(DMSO_d₆ and CF₃CO₂D) 1.7-1.9 (m, 2H), 2.15 (d, 2H), 2.37 (m, 1H), 3.1-3.35 (m, 6H), 3.6-3.7 (m, 6H), 3.8 (m, 4H), 4.05 (s, 3H), 4.2 (br s, 2H), 6.1 (s, 2H), 7.02 (s, 3H), 7.4 (s, 1H), 8.15 (s, 1H), 8.9 (s, 1H); Mass Spectrum: M+H⁺ 522.

The 4-chloro-6-methoxy-7-[N-(2-morpholinoethyl)piperidin-4-ylmethoxy]quinazoline used as a starting material was prepared as follows :-

A mixture of 7-(N-tert-butoxycarbonylpiperidin-4-ylmethoxy)-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (12 g), trifluoroacetic acid (25 ml) and methylene chloride (100 ml) was stirred at ambient temperature for 1.5 hours. The mixture was evaporated and the residue was partitioned between methylene chloride and a dilute aqueous sodium bicarbonate solution. The organic layer was washed with water and with brine, dried over magnesium sulphate and evaporated. The residue was triturated under a mixture of diethyl ether and pentane. The resultant solid was isolated and dried under vacuum. There was thus obtained 6-methoxy-7-piperidin-4-ylmethoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (9.1 g); NMR Spectrum: (DMSO_d₆) 1.15 (s, 9H), 1.2-1.35 (m, 2H), 1.78 (d, 2H), 1.95 (m, 1H), 2.6 (m, 2H), 3.05 (d, 2H), 3.9 (s, 3H), 4.0 (d, 2H), 5.92 (s, 2H), 7.14 (s, 1H), 7.5 (s, 1H), 8.34 (s, 1H); Mass Spectrum: M+H⁺ 404.

A mixture of a portion (1 g) of the material so obtained, 2-morpholinoethyl chloride hydrochloride salt (0.55 g), potassium iodide (0.21 g), sodium bicarbonate (0.625 g) and methanol (23 ml) was stirred and heated to reflux for 2.5 hours. The mixture was evaporated and the residue was partitioned between methylene chloride and water. The organic layer was washed with water and with brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 9:1 mixture of methylene chloride and a saturated methanolic ammonia solution as eluent. The residue was triturated under a mixture of diethyl ether and pentane. The resultant solid was isolated and dried under vacuum. There was thus obtained 6-methoxy-7-[N-(2-morpholinoethyl)piperidin-4-ylmethoxy]-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (0.42 g); NMR Spectrum: (DMSO_d₆) 1.15 (s, 9H), 1.25-1.4 (m, 2H), 1.7-1.9 (m, 3H), 1.9-2.1 (m, 2H), 2.4 (m, 8H), 2.95 (br s, 2H), 3.58 (m, 4H), 3.9 (s, 3H), 4.01 (d, 2H), 5.9 (s, 2H), 7.18 (s, 1H), 7.5 (s, 1H), 8.38 (s, 1H); Mass Spectrum: M+H⁺ 517.

A mixture of the material so obtained and a saturated methanolic ammonia solution (10 ml) was stirred at ambient temperature for 16 hours. The mixture was evaporated and the residue was triturated under a 4:1 mixture of diethyl ether and methylene chloride. The resultant solid was isolated, washed with diethyl ether and dried under vacuum. There was

thus obtained 6-methoxy-7-[N-(2-morpholinoethyl)piperidin-4-ylmethoxy]-3,4-dihydroquinazolin-4-one (0.29 g); NMR Spectrum: (DMSO_d₆) 1.25-1.4 (m, 2H), 1.7-1.85 (m, 3H), 1.9-2.1 (m, 2H), 2.4 (d, 8H), 2.92 (br s, 2H), 3.55 (m, 4H), 3.88 (s, 3H), 3.98 (d, 2H), 7.1 (s, 1H), 7.45 (s, 1H), 7.98 (s, 1H); Mass Spectrum: M+H⁺ 403.

- 5 A mixture of the material so obtained, thionyl chloride (5 ml) and DMF (0.05 ml) was heated to reflux for 1.5 hours. The mixture was evaporated, toluene was added and the mixture was evaporated. The residue was partitioned between methylene chloride and a cooled 2N aqueous sodium hydroxide solution. The organic layer was separated, washed with water and with brine, dried over magnesium sulphate and evaporated. There was thus 10 obtained 4-chloro-6-methoxy-7-[N-(2-morpholinoethyl)piperidin-4-ylmethoxy]quinazoline (0.115 g); NMR Spectrum: (DMSO_d₆) 1.25-1.4 (m, 2H), 1.7-1.9 (m, 3H), 1.98 (m, 2H), 2.4 (d, 8H), 2.92 (d, 2H), 3.55 (m, 4H), 4.02 (s, 3H), 4.1 (d, 2H), 7.4 (s, 1H), 7.45 (s, 1H), 8.88 (s, 1H); Mass Spectrum: M+H⁺ 421 and 423.

15 Example 3

7-hydroxy-6-methoxy-4-(2,3-methylenedioxyanilino)quinazoline

- A mixture of 7-benzyloxy-6-methoxy-4-(2,3-methylenedioxyanilino)quinazoline hydrochloride (21 g), ammonium formate (30.2 g), 10% palladium-on-charcoal catalyst (4.8 g), water (26 ml) and DMF (350 ml) was stirred at ambient temperature for 2 hours. The 20 mixture was filtered and the filtrate was evaporated. The residual oil was triturated under diethyl ether. The solid so obtained was triturated under water, collected by filtration, washed with water and with diethyl ether and dried under vacuum over phosphorus pentoxide. The material so obtained was purified by column chromatography on silica using a 9:1 mixture of methylene chloride and methanol as eluent. There was thus obtained the title compound 25 (15 g); NMR Spectrum: (DMSO_d₆) 3.95 (s, 3H), 6.0 (s, 2H), 6.85 (m, 2H), 6.95 (d, 1H), 7.05 (s, 1H), 7.8 (s, 1H), 8.3 (s, 1H), 9.4 (s, 1H), 10.3 (s, 1H); Mass Spectrum: M+H⁺ 312.

Example 4

4-(6-chloro-2,3-methylenedioxyanilino)-7-hydroxy-6-methoxyquinazoline

- 30 A mixture of 7-benzyloxy-4-(6-chloro-2,3-methylenedioxyanilino)-6-methoxyquinazoline dihydrochloride (3.3 g) and trifluoroacetic acid (60 ml) was heated to reflux for 4 hours. The mixture was evaporated. The residue was diluted with water and methanol and the mixture was basified to pH 7.5 by the addition of a saturated aqueous

sodium carbonate solution. The methanol was evaporated and the resultant solid was isolated and washed with water. There was thus obtained the title compound as a solid (2.5 g); NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 3.95 (s, 3H), 6.1 (s, 2H), 6.95 (d, 1H), 7.1 (m, 2H), 8.1 (s, 1H), 8.4 (s, 1H), 9.85 (br s, 1H), 10.7 (br s, 1H); Mass Spectrum: M+H⁺ 346 and 348.

5

Example 5

6-methoxy-4-(2,3-methylenedioxyanilino)-7-(3-methylsulphonylpropoxy)quinazoline monohydrochloride salt

- Diethyl azodicarboxylate (0.101 ml) was added dropwise to a stirred mixture of
- 10 7-hydroxy-6-methoxy-4-(2,3-methylenedioxyanilino)quinazoline (0.1 g), 3-methylsulphonylpropan-1-ol (0.057 g), triphenylphosphine (0.168 g) and methylene chloride (5 ml) and the reaction mixture was stirred at ambient temperature. After a few minutes further portions of triphenylphosphine (0.084 g) and 3-methylsulphonylpropan-1-ol (0.022 g) were added followed by the dropwise addition of diethyl azodicarboxylate (0.050 ml). After
- 15 another few minutes third portions of the same amounts of these reagents were added. The reaction mixture was evaporated and the residue was purified by column chromatography on silica using a 10:6:1 mixture of methylene chloride, ethyl acetate and methanol as eluent. The material so obtained was triturated under a 6M solution of hydrogen chloride in diethyl ether. There was thus obtained the title compound (0.108 g) as a white solid; NMR Spectrum:
- 20 (DMSO_d₆ and CF₃CO₂D) 2.3 (m, 2H), 3.05 (s, 3H), 3.35 (m, 2H), 4.0 (s, 3H), 4.35 (t, 2H), 6.1 (s, 2H), 7.0 (m, 3H), 7.3 (s, 1H), 8.1 (s, 1H), 8.15 (s, 1H); Mass Spectrum: M+H⁺ 432.

The 3-methylsulphonylpropan-1-ol used as a starting material was obtained as follows :-

- 3-Chloroperoxybenzoic acid (67%, 25 g) was added portionwise to a stirred mixture of
- 25 3-methylthiopropan-1-ol (5 ml) and methylene chloride and the resultant mixture was stirred at ambient temperature for 1 hour. The resultant mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography on alumina using a 19:1 mixture of methylene chloride and methanol as eluent to give the required starting material as an oil (4.18 g); NMR Spectrum: (CDCl₃) 2.1 (m, 2H), 2.96 (s, 3H), 3.2 (t, 2H), 3.8 (t, 2H);
- 30 Mass Spectrum: M+H⁺ 139.

Example 6

6,7-di-(2-methoxyethoxy)-4-(2,3-methylenedioxyanilino)quinazoline monohydrochloride salt

- Using an analogous procedure to that described in Example 1, 4-chloro-
5 6,7-di-(2-methoxyethoxy)quinazoline (US Patent No. 5,747,498; 0.1 g) was reacted with 2,3-methylenedioxyaniline (0.048 g) to give the title compound (0.121 g); NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 3.5 (s, 6H), 3.8 (m, 4H), 4.35 (m, 4H), 6.05 (s, 2H), 6.95 (m, 3H), 7.4 (s, 1H), 8.2 (s, 1H), 8.85 (s, 1H); Mass Spectrum: M+H⁺ 414.

10 **Example 7**

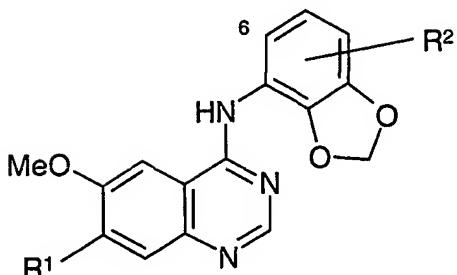
4-(6-chloro-2,3-methylenedioxyanilino)-6-methoxy-7-(2-pyrrolidin-1-ylethoxy)quinazoline

- Diethyl azodicarboxylate (0.182 ml) was added dropwise to a stirred mixture of 4-(6-chloro-2,3-methylenedioxyanilino)-7-hydroxy-6-methoxyquinazoline (0.2 g),
15 N-(2-hydroxyethyl)pyrrolidine (0.086 g), triphenylphosphine (0.303 g) and methylene chloride (3 ml) and the reaction mixture was stirred at ambient temperature for 15 minutes. The reaction mixture was evaporated and the residue was purified by column chromatography on silica using a 45:4:1 mixture of methylene chloride, methanol and a saturated methanolic ammonia solution as eluent. There was thus obtained the title compound (0.033 g) as a white
20 solid; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 1.9 (m, 2H), 2.1 (m, 2H), 3.2 (m, 2H), 3.7 (m, 2H), 3.8 (m, 2H), 4.05 (s, 3H), 4.6 (m, 2H), 6.2 (s, 2H), 7.1 (d, 1H), 7.2 (d, 1H), 7.5 (s, 1H), 8.2 (s, 1H), 8.95 (s, 1H); Mass Spectrum: M-H⁻ 441 and 443.

Example 8

- 25 Using an analogous procedure to that described in Example 7, the appropriate 7-hydroxyquinazoline was reacted with the appropriate alcohol to give the compounds described in Table II. Unless otherwise stated, each compound described in Table II was obtained as the free base.

Table II



Compound No. & Note	R ¹	R ²
[1]	3-diisopropylaminoproxy	hydrogen
[2]	3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy	6-chloro
[3]	3-piperidinoproxy	6-chloro
[4]	3-methylsulphonylpropoxy	6-chloro
[5]	3-diisopropylaminoproxy	6-chloro
[6]	2-(4-methylpiperazin-1-yl)ethoxy	hydrogen
[7]	2-piperidinoethoxy	6-chloro
[8]	2-(4-methylpiperazin-1-yl)ethoxy	6-chloro
[9]	2-pyrrol-1-yloxy	6-chloro
[10]	2-(2-oxopyrrolidin-1-yl)ethoxy	6-chloro
[11]	2-(4-pyridyloxy)ethoxy	6-chloro
[12]	3-(4-pyridyloxy)propoxy	6-chloro
[13]	3-(4-pyridyloxy)propoxy	hydrogen
[14]	3-(6-methylpyrid-2-yloxy)propoxy	hydrogen
[15]	3-(6-methylpyrid-2-yloxy)propoxy	6-chloro
[16]	3-(2-pyridyloxy)propoxy	hydrogen
[17]	3-(2-pyridyloxy)propoxy	6-chloro
[18]	2-(6-chloropyrid-2-yloxy)ethoxy	hydrogen
[19]	2-(6-chloropyrid-2-yloxy)ethoxy	6-chloro
[20]	2-cyanopyrid-4-ylmethoxy	6-chloro
[21]	2-cyanopyrid-4-ylmethoxy	hydrogen

[22]	2-(<i>N</i> - <i>tert</i> -butoxycarbonyl-4-hydroxypiperidin-4-yl)ethoxy	hydrogen
[23]	2-(4-hydroxytetrahydropyran-4-yl)ethoxy	hydrogen
[24]	2-(4-hydroxytetrahydropyran-4-yl)ethoxy	6-chloro
[25]	ethoxy	hydrogen
[26]	3-(4- <i>tert</i> -butoxycarbonylpiperazin-1-yl)propoxy	6-chloro
[27]	3-(4- <i>tert</i> -butoxycarbonylpiperazin-1-yl)propoxy	hydrogen
[28]	2-(4-pyridyloxy)ethoxy	hydrogen
[29]	<i>N</i> - <i>tert</i> -butoxycarbonylpiperidin-4-ylmethoxy	6-chloro
[30]	3-(<i>cis</i> -4-cyanomethyl-3,5-dimethylpiperazin-1-yl)propoxy	hydrogen
[31]	3-(<i>cis</i> -3,5-dimethylpiperazin-1-yl)propoxy	hydrogen
[32]	3-(4-mesylpiperazin-1-yl)propoxy	6-chloro
[33]	3-[4-(2-cyanoethyl)piperazin-1-yl]propoxy	6-chloro
[34]	3-(4-isobutyrylpiperazin-1-yl)propoxy	6-chloro

Notes

[1] The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 1.3 (m, 12H), 2.25 (m, 2H), 3.4 (m, 2H), 3.8 (m, 2H), 4.0 (s, 3H), 4.3 (t, 2H), 6.1 (s, 2H), 7.0 (m, 3H), 7.35 (s, 1H), 8.1 (s, 1H), 8.9 (s, 1H); Mass Spectrum: M+H⁺ 453.

The 3-diisopropylaminopropan-1-ol used as a starting material was prepared as described in Tet. Lett., 1994, 35, 761.

[2] The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 2.35 (m, 2H), 3.5 (m, 2H), 3.65 (m, 4H), 3.85 (m, 4H), 4.05 (s, 3H), 4.35 (m, 2H), 6.15 (s, 2H), 7.05 (d, 1H), 7.15 (d, 1H), 7.4 (s, 1H), 8.15 (s, 1H), 8.9 (s, 1H); Mass Spectrum: M+H⁺ 521 and 523.

[3] The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 1.4 (m, 1H), 1.7 (m, 3H), 1.85 (m, 2H), 2.3 (m, 2H), 2.95 (m, 2H), 3.3 (m, 2H), 3.55 (m, 2H), 4.05 (s, 3H), 4.3 (m, 2H), 6.15 (s, 2H), 7.05 (d, 1H), 7.15 (d, 1H), 7.4 (s, 1H), 8.15 (s, 1H), 8.95 (s, 1H); Mass Spectrum: M+H⁺ 471 and 473.

[4] The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 2.3 (m, 2H), 3.05 (s, 3H), 3.35 (m, 2H), 4.05 (s, 3H), 4.35 (m, 2H), 6.15 (s, 2H),

7.05 (d, 1H), 7.15 (d, 1H), 7.35 (s, 1H), 8.15 (s, 1H), 8.9 (s, 1H); Mass Spectrum: M+H⁺ 466 and 468.

[5] The product gave the following characterising data; NMR Spectrum: (DMSO_d₆) 0.95 (d, 12H), 1.85 (m, 2H), 2.6 (m, 2H), 3.0 (m, 2H), 3.95 (s, 3H), 4.15 (m, 2H), 6.1 (s, 2H), 6.95 5 (d, 1H), 7.05 (d, 1H), 7.15 (s, 1H), 7.8 (s, 1H), 8.3 (s, 1H), 9.45 (s, 1H); Mass Spectrum: M-H⁻ 485 and 487.

[6] The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 2.9 (s, 3H), 3.3-3.9 (br s, 8H), 3.8 (m, 2H), 4.0 (s, 3H), 4.6 (m, 2H), 6.1 (s, 2H), 7.0 (m, 3H), 7.45 (s, 1H), 8.15 (s, 1H), 8.9 (s, 1H); Mass Spectrum: M+H⁺ 438; Elemental Analysis: Found C, 61.75; H, 6.24; N, 15.6; C₂₃H₂₇N₅O₄ 0.5H₂O requires C, 61.87; H, 6.32; N, 15.68%.

The 1-(2-hydroxyethyl)-4-methylpiperazine used as a starting material was prepared as follows :-

A mixture of 2-bromoethanol (2.36 g), N-methylpiperazine (1.26 g), potassium 15 carbonate (5.0 g) and ethanol (150 ml) was stirred and heated to reflux for 18 hours. The mixture was cooled to ambient temperature and filtered. The filtrate was evaporated and the residue was triturated under a mixture of methylene chloride and acetone. The resultant mixture was filtered and the filtrate was evaporated to give the required starting material as an oil (0.87 g); NMR Spectrum: (CDCl₃) 2.18 (s, 3H), 2.3-2.7 (br m, 8H), 2.56 (t, 2H), 3.61 (t, 20 2H).

[7] The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 1.4 (m, 1H), 1.7 (m, 3H), 1.85 (m, 2H), 3.1 (m, 2H), 3.6 (m, 2H), 3.7 (m, 2H), 4.05 (s, 3H), 4.6 (m, 2H), 6.15 (s, 2H), 7.05 (d, 1H), 7.15 (d, 1H), 7.45 (s, 1H), 8.15 (s, 1H), 8.95 (s, 1H); Mass Spectrum: M+H⁺ 455 and 457.

[8] The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 2.9 (s, 3H), 3.3-3.9 (br s, 8H), 3.75 (m, 2H), 4.05 (s, 3H), 4.6 (m, 2H), 6.15 (s, 2H), 7.05 (d, 1H), 7.15 (d, 1H), 7.5 (s, 1H), 8.2 (s, 1H), 8.9 (s, 1H); Mass Spectrum: M+H⁺ 472 and 474.

[9] The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 4.05 (s, 3H), 4.4 (m, 2H), 4.5 (m, 2H), 6.05 (d, 2H), 6.15 (s, 2H), 6.9 (d, 2H), 7.05 (d, 1H), 7.15 (d, 1H), 7.3 (s, 1H), 8.15 (s, 1H), 8.9 (s, 1H); Mass Spectrum: M+H⁺ 439 and 441.

The 2-pyrrol-1-ylethanol used as a starting material was prepared using an analogous procedure to that described in J.C.S. Chem. Comm., 1974, 931.

[10] The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 1.95 (m, 2H), 2.25 (t, 2H), 3.5 (t, 2H), 3.65 (t, 2H), 3.95 (s, 3H), 4.25 (t, 2H), 6.1 (s, 2H), 6.95 (d, 1H), 7.05 (d, 1H), 7.2 (s, 1H), 7.85 (s, 1H), 8.3 (s, 1H), 9.45 (s, 1H); Mass Spectrum: M+H⁺ 457 and 459.

[11] The product gave the following characterising data; NMR Spectrum: (DMSO_d₆) 3.95 (s, 3H), 4.5 (m, 4H), 6.05 (s, 2H), 6.95 (d, 1H), 7.05 (m, 3H), 7.25 (s, 1H), 7.85 (s, 1H), 8.35 (s, 1H), 8.4 (d, 2H), 9.5 (s, 1H); Mass Spectrum: M+H⁺ 467 and 469.

10 The 4-(2-hydroxyethoxy)pyridine used as a starting material was prepared according to the procedure disclosed in J. Chem. Soc. Perkin II, 1987, 1867.

[12] The product gave the following characterising data; NMR Spectrum: (DMSO_d₆) 2.3 (m, 2H), 3.9 (s, 3H), 4.3 (m, 4H), 6.05 (s, 2H), 6.95 (d, 1H), 7.0 (d, 2H), 7.05 (d, 1H), 7.25 (s, 1H), 7.85 (s, 1H), 8.3 (s, 1H), 8.4 (d, 2H), 9.45 (s, 1H); Mass Spectrum: M+H⁺ 481 and 483.

15 The 4-(3-hydroxypropoxy)pyridine used as a starting material was prepared as follows :-

Sodium hydroxide (6.66 g) was added to a mixture of 4-chloropyridine hydrochloride (10 g), 1,3-propanediol (24 ml) and DMSO (100 ml) and the mixture was stirred and heated to 100°C for 20 hours. The mixture was concentrated by evaporation under vacuum of DMSO (about 80 ml) and the residual mixture was diluted with ice-water and extracted with ethyl acetate (4x). The organic phases were combined, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 12:7:1 mixture of methylene chloride, ethyl acetate and methanol as eluent. There was thus obtained 4-(3-hydroxypropoxy)pyridine (3.13 g) as an oil; NMR Spectrum: (CDCl₃) 2.05 (m, 2H), 3.0 (br s, 1H), 3.85 (m, 2H), 4.15 (t, 2H), 6.75 (d, 2H), 8.35 (d, 2H); Mass Spectrum: M+H⁺ 154.

[13] DMF was used in place of methylene chloride as the reaction solvent. The product gave the following characterising data; NMR Spectrum: (DMSO_d₆) 2.3 (m, 2H), 3.95 (s, 3H), 4.3 (m, 4H), 6.05 (s, 2H), 6.85 (m, 2H), 6.95 (d, 1H), 7.05 (d, 2H), 7.2 (s, 1H), 7.8 (s, 1H), 8.35 (s, 1H), 8.4 (d, 2H), 9.5 (s, 1H); Mass Spectrum: M-H⁻ 445.

30 [14] The product gave the following characterising data; NMR Spectrum: (DMSO_d₆) 2.25 (m, 2H), 2.4 (s, 3H), 3.95 (s, 3H), 4.3 (t, 2H), 4.45 (t, 2H), 6.1 (s, 2H), 6.65 (d, 1H), 6.85 (m, 3H), 6.95 (d, 1H), 7.2 (s, 1H), 7.6 (t, 1H), 7.85 (s, 1H), 8.35 (s, 1H), 9.5 (s, 1H); Mass Spectrum: M+H⁺ 461.

The 2-(3-hydroxypropoxy)-6-methylpyridine used as a starting material was prepared as follows :-

Sodium hydroxide (3 g) was added to a mixture of 6-chloro-2-methylpyridine (3.3 ml), 1,3-propanediol (11 ml) and DMSO (35 ml) and the mixture was stirred and heated to 100°C 5 for 20 hours. The mixture was cooled to ambient temperature, diluted with ice-water and extracted with ethyl acetate (3x). The organic phases were combined, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 4:1 mixture of methylene chloride and ethyl acetate as eluent. There was thus obtained 2-(3-hydroxypropoxy)-6-methylpyridine (3.5 g) as an oil; NMR Spectrum: (CDCl₃) 1.95 (m, 10 2H), 2.45 (s, 3H), 3.7 (m, 2H), 4.1 (br s, 1H), 4.5 (t, 2H), 6.55 (d, 1H), 6.75 (d, 1H), 7.45 (t, 1H).

[15] The product gave the following characterising data; NMR Spectrum: (DMSO_d₆) 2.25 (m, 2H), 2.4 (s, 3H), 3.95 (s, 3H), 4.3 (t, 2H), 4.45 (t, 2H), 6.1 (s, 2H), 6.65 (d, 1H), 6.85 (d, 1H), 6.95 (d, 1H), 7.1 (d, 1H), 7.25 (s, 1H), 7.6 (t, 1H), 7.85 (s, 1H), 8.35 (s, 1H), 9.5 (s, 1H); 15 Mass Spectrum: M+H⁺ 495 and 497.

[16] DMF was used in place of methylene chloride as the reaction solvent. The product gave the following characterising data; NMR Spectrum: (DMSO_d₆) 2.2 (m, 2H), 3.95 (s, 3H), 4.1 (t, 2H), 4.2 (t, 2H), 6.05 (s, 2H), 6.2 (t, 1H), 6.4 (d, 1H), 6.9 (m, 2H), 6.95 (d, 1H), 7.15 (s, 1H), 7.4 (m, 1H), 7.7 (d, 1H), 7.85 (s, 1H), 8.4 (s, 1H), 9.6 (s, 1H); Mass Spectrum: M+H⁺ 20 447.

The 2-(3-hydroxypropoxy)pyridine used as a starting material was prepared by the reaction of 2-chloropyridine and 1,3-propanediol using an analogous procedure to that described in Note [14] immediately above.

[17] DMF was used in place of methylene chloride as the reaction solvent. The product 25 gave the following characterising data; NMR Spectrum: (DMSO_d₆) 2.2 (m, 2H), 3.95 (s, 3H), 4.1 (t, 2H), 4.2 (t, 2H), 6.1 (s, 2H), 6.2 (t, 1H), 6.4 (d, 1H), 6.95 (d, 1H), 7.1 (d, 1H), 7.2 (s, 1H), 7.4 (m, 1H), 7.65 (d, 1H), 7.85 (s, 1H), 8.35 (s, 1H), 9.5 (s, 1H); Mass Spectrum: M+H⁺ 481 and 483.

[18] DMF was used in place of methylene chloride as the reaction solvent. The reaction 30 product was purified by column chromatography on silica (Isolute SCX column) using an 18:1 mixture of methylene chloride and a saturated methanolic ammonia solution as eluent. The product so obtained gave the following characterising data; NMR Spectrum: (DMSO_d₆) 3.95

(s, 3H), 4.5 (m, 2H), 4.65 (m, 2H), 6.05 (s, 2H), 6.9 (m, 4H), 7.15 (d, 1H), 7.25 (s, 1H), 7.8 (m, 2H), 8.4 (s, 1H), 9.5 (s, 1H); Mass Spectrum: M+H⁺ 467 and 469.

The 6-chloro-2-(2-hydroxyethoxy)pyridine used as a starting material was prepared as follows :-

- 5 Sodium hydride (50% dispersion in mineral oil; 0.48 g) was added portionwise to a stirred mixture of 2-tetrahydropyran-2-yloxyethanol (1.36 ml) and DMF (5 ml) and the mixture was stirred at ambient temperature for 30 minutes and then heated to 80°C for 15 minutes. The mixture was cooled to ambient temperature. 2,6-Dichloropyridine (1.48 g) was added and the resultant mixture was heated to 80°C for 16 hours. The mixture was
10 cooled to ambient temperature and partitioned between ethyl acetate and water. The organic phase was washed with brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using methylene chloride as eluent. There was thus obtained 2-chloro-6-(2-tetrahydropyran-2-yloxyethoxy)pyridine (2 g) as an oil; NMR Spectrum: (CDCl₃) 1.4-1.9 (m, 6H), 3.5 (m, 1H), 3.75 (m, 1H), 3.85 (m, 1H), 4.05 (m, 1H),
15 4.5 (m, 2H), 4.7 (m, 1H), 6.7 (d, 1H), 6.9 (d, 1H), 7.5 (t, 1H).

- A mixture of the material so obtained, acetic acid (20 ml), water (4 ml) and THF (8 ml) was stirred and heated to 80°C for 5 hours. The solvent was evaporated and the residue was purified by column chromatography on silica using a 3:2 mixture of petroleum ether (b.p. 40-60°C) and diethyl ether as eluent. There was thus obtained 6-chloro-
20 2-(2-hydroxyethoxy)pyridine (0.98 g) as an oil; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D): 2.5 (br s, 1H), 3.9 (m, 2H), 4.45 (m, 2H), 6.7 (d, 1H), 6.9 (d, 1H), 7.5 (t, 1H); Mass Spectrum: M+H⁺ 174 and 176.

- [19] The reaction product was purified by column chromatography on silica (Isolute SCX column) using an 18:1 mixture of methylene chloride and a saturated methanolic ammonia
25 solution as eluent. The product so obtained gave the following characterising data; NMR Spectrum: (DMSO_d₆) 4.05 (s, 3H), 4.5 (m, 2H), 4.65 (m, 2H), 6.1 (s, 2H), 6.9 (t, 2H), 7.05 (d, 1H), 7.15 (d, 1H), 7.3 (s, 1H), 7.8 (t, 1H), 7.85 (s, 1H), 8.35 (s, 1H), 9.5 (br s, 1H); Mass Spectrum: M+H⁺ 501 and 503.

- [20] The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and
30 CF₃CO₂D) 4.05 (s, 3H), 5.55 (s, 2H), 6.15 (s, 2H), 7.05 (d, 1H), 7.15 (d, 1H), 7.35 (s, 1H), 7.85 (d, 1H), 8.14 (s, 1H), 8.18 (s, 1H), 8.85 (d, 1H), 8.9 (s, 1H); Mass Spectrum: M+H⁺ 462 and 464.

The 2-cyano-4-hydroxymethylpyridine used as a starting material was prepared as follows :-

Using an analogous procedure to that disclosed in J. Het. Chem., 1993, 30, 631, 4-hydroxymethylpyridine was converted into 4-(tert-butyldimethylsilyloxymethyl)pyridine-2-5 carbonitrile.

- A mixture of the material so obtained (3.37 g) tert-butylammonium fluoride (1M solution in THF; 24 ml) and THF (20 ml) was stirred at ambient temperature for 1 hour. The mixture was evaporated and the residue was partitioned between ethyl acetate and a saturated aqueous ammonium chloride solution. The organic phase was washed with water and with 10 brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of petroleum ether (b.p. 40-60°C) and ethyl acetate as eluent. There was thus obtained 2-cyano-4-hydroxymethylpyridine as a solid (1.37 g); NMR Spectrum: (CDCl₃) 2.25 (br s, 1H), 4.85 (s, 2H), 7.55 (d, 1H), 7.75 (s, 1H), 8.7 (d, 1H).
- 15 [21] DMF was used in place of methylene chloride as the reaction solvent. The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 4.0 (s, 3H), 5.45 (s, 2H), 6.0 (s, 2H), 6.85-7.0 (m, 3H), 7.3 (s, 1H), 7.85 (d, 1H), 7.9 (s, 1H), 8.1 (s, 1H), 8.4 (s, 1H), 8.8 (d, 1H); Mass Spectrum: M+H⁺ 428.
- [22] The product gave the following characterising data; NMR Spectrum: (CDCl₃) 1.45 (s, 9H), 1.6 (m, 4H), 2.1 (m, 2H), 3.2 (s, 1H), 3.25 (m, 2H), 3.8 (m, 2H), 4.0 (s, 3H), 4.4 (t, 2H), 6.05 (s, 2H), 6.7 (d, 1H), 6.9 (t, 1H), 7.0 (s, 1H), 7.05 (s, 1H), 7.25 (s, 1H), 7.75 (d, 1H), 8.7 (s, 1H); Mass Spectrum: M+H⁺ 539.

The N-tert-butoxycarbonyl-4-hydroxy-4-(2-hydroxyethyl)piperidine used as a starting material was prepared as follows :-

- 25 A mixture of tert-butyl 4-oxopiperidine-1-carboxylate (5 g), ethyl bromoacetate (4.17 ml), zinc powder (2.46 g) and THF (40 ml) was stirred and heated to reflux to initiate reaction. Once the reaction had started, the temperature of the reaction mixture was controlled by the occasional immersion of the mixture in an ice bath. After 2 hours the reaction mixture was evaporated and the residue was partitioned between ethyl acetate and water. The organic 30 phase was washed with brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 6:1 mixture of methylene chloride and ethyl acetate as eluent. There was thus obtained tert-butyl 4-ethoxycarbonylmethyl-4-hydroxypiperidine-1-carboxylate as an oil (6.5 g); NMR Spectrum: (CDCl₃) 1.3 (t, 3H), 1.45

(s, 9H), 1.5 (m, 2H), 1.7 (m, 2H), 2.5 (s, 2H), 3.2 (m, 2H), 3.6 (s, 1H), 3.85 (br s, 2H), 4.2 (m, 2H).

A solution of the material so obtained in THF (30 ml) was added to a stirred suspension of lithium aluminium hydride (0.86 g) in THF (45 ml) which was cooled in an ice-
5 bath to 0°C. After completion of the addition, the reaction mixture was heated to reflux for 2 hours. The mixture was cooled to 0°C and a concentrated (40%) aqueous sodium hydroxide solution was added. The mixture was filtered and the filtrate was concentrated by partial evaporation. The residue was extracted with methylene chloride and the extract was dried over magnesium sulphate and evaporated. There was thus obtained N-tert-butoxycarbonyl-
10 4-hydroxy-4-(2-hydroxyethyl)piperidine as an oil; NMR Spectrum: (CDCl₃) 1.45 (s, 9H), 1.5 (m, 2H), 1.7 (m, 2H), 1.75 (m, 2H), 2.2 (br s, 1H), 2.9 (s, 1H), 3.2 (m, 2H), 3.75 (m, 2H), 3.95 (m, 2H).

[23] The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 1.5 (m, 2H), 1.65 (m, 2H), 2.0 (m, 2H), 3.65 (m, 4H), 4.0 (s, 3H), 4.35 (t, 2H),
15 6.05 (s, 2H), 7.0 (m, 3H), 7.35 (s, 1H), 8.05 (s, 1H), 8.85 (s, 1H); Mass Spectrum: M+H⁺ 440.

The 4-hydroxy-4-(2-hydroxyethyl)tetrahydropyran used as a starting material was prepared as follows :-

Using analogous procedures to those described in Note [22] immediately above for the conversion of tert-butyl 4-oxopiperidine-1-carboxylate into N-tert-butoxycarbonyl-4-hydroxy-
20 4-(2-hydroxyethyl)piperidine, tetrahydropyran-4-one was reacted with ethyl bromoacetate to give ethyl 2-(4-hydroxytetrahydropyran-4-yl)acetate; NMR Spectrum: (CDCl₃) 1.3 (t, 3H), 1.65 (m, 4H), 2.5 (s, 2H), 4.6 (s, 1H), 3.75 (m, 2H), 3.85 (m, 2H), 4.2 (q, 2H); which, in turn, was reduced to give 4-hydroxy-4-(2-hydroxyethyl)tetrahydropyran; NMR Spectrum: (CDCl₃) 1.7 (m, 4H), 1.8 (m, 2H), 2.25 (br s, 1H), 2.9 (br s, 1H), 3.8 (m, 4H), 3.95 (m, 2H).

25 [24] The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 1.5 (m, 2H), 1.65 (m, 2H), 2.0 (m, 2H), 3.6 (m, 4H), 4.0 (m, 5H), 6.15 (s, 2H), 7.05 (d, 1H), 7.15 (d, 1H), 7.35 (s, 1H), 8.1 (s, 1H), 8.9 (s, 1H); Mass Spectrum: M+H⁺ 474 and 476.

[25] Chloroform was used in place of methylene chloride as the reaction solvent. The
30 product gave the following characterising data; NMR Spectrum: (DMSO_d₆) 1.45 (t, 3H), 3.95 (s, 3H), 4.2 (q, 2H), 6.05 (s, 2H), 6.9 (m, 2H), 6.95 (d, 1H), 7.15 (s, 1H), 7.8 (s, 1H), 8.35 (s, 1H), 9.5 (s, 1H); Mass Spectrum: M+H⁺ 340.

[26] The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 1.4 (s, 9H), 2.05 (m, 2H), 2.45 (m, 4H), 2.6 (m, 2H), 3.35 (m, 4H), 3.95 (s, 3H), 4.2 (m, 2H), 6.1 (s, 2H), 6.95 (d, 1H), 7.05 (d, 1H), 7.2 (s, 1H), 7.85 (s, 1H), 8.3 (s, 1H); Mass Spectrum: M+H⁺ 572 and 574.

5 The 1-(tert-butoxycarbonyl)-4-(3-hydroxypropyl)piperazine used as a starting material was prepared as follows using an analogous procedure to that described in European Patent Application No. 0388309 :-

A mixture of 3-bromopropanol (25 ml), 1-(tert-butoxycarbonyl)piperazine (29 ml), potassium carbonate (83 g) and ethanol (200 ml) was stirred and heated to reflux for 20 hours.

10 The mixture was cooled to ambient temperature and filtered. The filtrate was evaporated and the residue was triturated under diethyl ether. The resultant mixture was filtered and the filtrate was evaporated. The residue was purified by distillation to give the required starting material as an oil.

[27] The product gave the following characterising data; NMR Spectrum: (DMSO_d₆) 1.4 (s, 15 9H), 1.95 (m, 2H), 2.35 (m, 4H), 2.45-2.6 (m, 6H), 3.95 (s, 3H), 4.2 (t, 2H), 6.05 (s, 2H), 6.8-7.0 (m, 3H), 7.2 (s, 1H), 7.8 (s, 1H), 8.35 (s, 1H), 9.5 (s, 1H); Mass Spectrum: M+H⁺ 538.

[28] The free base form of the reaction product was treated with a 6M solution of hydrogen chloride in diethyl ether to give the dihydrochloride salt which gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 4.0 (s, 3H), 4.68 (br s, 2H), 4.9 (br s, 2H), 6.1 (s, 2H), 7.0 (2s, 2H), 7.5 (s, 1H), 7.7 (d, 2H), 8.2 (s, 1H), 8.85 (d, 2H), 8.9 (s, 1H); Mass Spectrum: M+H⁺ 433.

[29] DMF was used in place of methylene chloride as the reaction solvent. The product gave the following characterising data; Mass Spectrum: M+H⁺ 543 and 545.

[30] DMF was used in place of methylene chloride as the reaction solvent and the reaction 25 mixture was stirred at ambient temperature for 16 hours. The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 1.12 (s, 3H), 1.13 (s, 3H), 2.3 (m, 2H), 2.8 (m, 4H), 3.3 (m, 2H), 3.65 (d, 2H), 4.0 (s, 3H), 4.05 (s, 2H), 4.35 (m, 2H), 6.1 (s, 2H), 7.0 (m, 3H), 7.35 (s, 1H), 8.1 (s, 1H), 8.9 (s, 1H); Mass Spectrum: M+H⁺ 505.

The cis-3,5-dimethyl-4-cyanomethyl-1-(3-hydroxypropyl)piperazine used as a starting 30 material was prepared as follows :-

A mixture of cis-2,6-dimethylpiperazine (4.3 g), 3-bromopropanol (5.2 g), potassium carbonate (15.6 g) and acetonitrile (30 ml) was stirred and heated to 80°C for 2.5 hours. The mixture was filtered and the filtrate was evaporated. The residue was purified

by column chromatography on silica using a 21:1 mixture of methylene chloride and a saturated methanolic ammonia solution as eluent. There was thus obtained cis-3,5-dimethyl-1-(3-hydroxypropyl)piperazine (5.84 g).

- A mixture of a portion (2.5 g) of the material so obtained, trityl chloride (4.25 g),
5 4-dimethylaminopyridine (0.018 g), triethylamine (2.2 ml) and DMF (40 ml) was stirred and heated to 40°C for 5 hours. The mixture was evaporated and the residue was partitioned between ethyl acetate and water. The organic phase was washed with water and with brine, dried over magnesium sulphate and evaporated to give cis-3,5-dimethyl-1-(3-trityloxypropyl)piperazine as a foam (5 g); NMR Spectrum: (DMSO_d₆ and CD₃CO₂D)
10 1.18 (s, 3H), 1.2 (s, 3H), 1.7 (m, 2H), 1.95 (m, 2H), 2.45 (m, 2H), 2.9 (m, 2H), 3.05 (t, 2H), 3.15 (m, 2H), 7.2-7.5 (m, 15H).

- A mixture of the material so obtained, 2-bromoacetonitrile (0.925 ml), potassium carbonate (5 g), tri-n-butylammonium iodide (0.44 g) and DMF (12 ml) was stirred and heated to 40°C for 6 hours. The mixture was filtered and the filtrate was evaporated. The residue
15 was partitioned between ethyl acetate and water. The organic phase was washed with water and with brine, dried over magnesium sulphate and evaporated. The material so obtained was purified by column chromatography on silica a 17:3 mixture of methylene chloride and methanol as eluent. There was thus obtained cis-3,5-dimethyl-4-cyanomethyl-1-(3-trityloxypropyl)piperazine (2.7 g) as a gum.

- 20 A mixture of cis-3,5-dimethyl-4-cyanomethyl-1-(3-trityloxypropyl)piperazine (3 g), a 1N aqueous hydrochloric acid solution (20 ml) and methanol (100 ml) was stirred at ambient temperature for 17 hours. The solvent was evaporated and the residual aqueous solution was basified to pH 11 by the addition of a saturated aqueous sodium carbonate solution. The mixture was extracted with ethyl acetate and the organic phase was washed
25 with water and with brine, dried and evaporated. The material so obtained was purified by column chromatography on silica using a 9:1 mixture of methylene chloride and methanol as eluent. There was thus obtained cis-3,5-dimethyl-4-cyanomethyl-1-(3-hydroxypropyl)piperazine as a gum (0.4 g); NMR Spectrum: (CDCl₃) 1.07 (s, 3H), 1.09 (s, 3H), 1.75 (m, 2H), 1.9 (t, 2H), 2.55 (t, 2H), 2.7 (m, 2H), 2.95 (d, 2H), 3.75 (s, 2H), 3.8 (t, 30 2H).

[31] The reaction mixture was stirred at ambient temperature for 5 hours. The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 1.28 (s, 3H), 1.3

(s, 3H), 2.35 (m, 2H), 3.05 (t, 2H), 3.4 (m, 2H), 3.65 (m, 2H), 3.9 (d, 2H), 4.0 (s, 3H), 4.3 (t, 2H), 6.1 (s, 2H), 7.0 (m, 3H), 7.4 (s, 1H), 8.1 (s, 1H), 8.9 (s, 1H); Mass Spectrum: M+H⁺ 466.

- [32] The reaction mixture was stirred at ambient temperature for 1 hour. The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 2.3 (m, 2H), 3.05 (s, 3H), 3.1-3.3 (m, 4H), 3.4 (t, 2H), 3.6-3.9 (m, 4H), 4.05 (s, 3H), 4.35 (t, 2H), 6.15 (s, 2H), 7.1 (d, 1H), 7.2 (d, 1H), 7.4 (s, 1H), 8.15 (s, 1H), 8.9 (s, 1H); Mass Spectrum: M+H⁺ 550.

The 1-(3-hydroxypropyl)-4-mesylpiperazine used as a starting material was prepared as follows :-

- 10 Mesyl chloride (0.966 ml) was added dropwise to a stirred mixture of 1-benzylpiperazine (2 g), triethylamine (1.74 ml) and methylene chloride (30 ml) which was cooled to 0°C. The reaction mixture was allowed to warm to ambient temperature and stirred for 1 hour. The mixture was partitioned between methylene chloride and water. The organic phase was washed with water and with brine, dried over magnesium sulphate and evaporated.
- 15 The residue was purified by column chromatography on silica using a 7:3 mixture of methylene chloride and ethyl acetate as eluent. There was thus obtained 1-benzyl-4-mesylpiperazine (2.5 g) as a solid; NMR Spectrum: (CDCl₃) 2.6 (m, 4H), 2.8 (s, 3H), 3.3 (m, 4H), 3.55 (s, 2H), 7.3 (m, 5H); Mass Spectrum: M+H⁺ 255.

A mixture of the material so obtained, cyclohexene (30 ml), palladium oxide on charcoal catalyst (20%; 0.5 g) and ethanol (70 ml) was stirred and heated to 80°C for 4 hours. The catalyst was removed by filtration and the solvent was evaporated to give 1-mesylpiperazine (1.58 g) as a solid; NMR Spectrum: (CDCl₃) 2.8 (s, 3H), 3.0 (m, 4H), 3.2 (m, 4H); Mass Spectrum: M+H⁺ 165.

- 20 A mixture of the material so obtained, 3-bromopropanol (1.13 ml), potassium carbonate (1.73 g) and acetonitrile (10 ml) was stirred and heated to 40°C for 4 hours and then to 70°C for 2 hours. The excess of potassium carbonate was removed by filtration and the filtrate was evaporated. The residue was purified by column chromatography on silica using increasingly polar solvent mixtures of methylene chloride and methanol as eluent. There was thus obtained 1-(3-hydroxypropyl)-4-mesylpiperazine (1.95 g) as a solid; NMR Spectrum: (CDCl₃) 1.8 (m, 2H), 2.6-2.7 (m, 6H), 2.8 (s, 3H), 3.3 (m, 4H), 3.8 (t, 2H), 4.5 (br s, 1H); Mass Spectrum: M+H⁺ 223.

- [33] The reaction mixture was stirred at ambient temperature for 5 hours. The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 2.3 (m, 2H),

2.95 (t, 2H), 3.2 (t, 2H), 3.4 (t, 2H), 2.9-3.7 (br m, 8H), 4.05 (s, 3H), 4.35 (t, 2H), 6.2 (s, 2H), 7.05 (d, 1H), 7.15 (d, 1H), 7.4 (s, 1H), 8.15 (s, 1H), 8.9 (s, 1H); Mass Spectrum: M+H⁺ 525.

The 3-[4-(3-hydroxypropyl)piperazin-1-yl]propionitrile used as a starting material was prepared as follows :-

- 5 Acrylonitrile (0.827 ml) was added to a mixture of 1-benzylpiperazine (2 g), methylene chloride (20 ml) and methanol (20 ml) and the resultant mixture was stirred at ambient temperature for 24 hours. The mixture was evaporated and the residue was purified by column chromatography on silica using a 97:3 mixture of methylene chloride and methanol as eluent. There was thus obtained 3-(4-benzylpiperazin-1-yl)propionitrile (2.63 g) as a liquid;
- 10 NMR Spectrum: (CDCl₃) 2.5 (m, 10H), 2.7 (t, 2H), 3.55 (s, 2H), 7.3 (m, 5H); Mass Spectrum: M+H⁺ 230.

The material so obtained was treated according to the procedures described in the last two paragraphs of the portion of Note [32] immediately above that is concerned with the preparation of starting materials. There was thus obtained 3-[4-(3-hydroxypropyl)piperazin-1-yl]propionitrile as a liquid (1.36 g); NMR Spectrum: (CDCl₃) 1.7 (m, 2H), 2.3-2.7 (m, 14H), 3.8 (t, 2H); Mass Spectrum: M+H⁺ 198.

- [34] The reaction mixture was stirred at ambient temperature for 5 hours. The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 0.95 (d, 6H), 2.05 (t, 2H), 2.45 (m, 4H), 2.6 (m, 2H), 2.85 (m, 1H), 3.5 (m, 4H), 3.95 (s, 3H), 4.2 (t, 2H), 6.05 (s, 2H), 6.9 (d, 1H), 7.05 (d, 1H), 7.2 (s, 1H), 7.85 (s, 1H), 8.3 (s, 1H); Mass Spectrum: M+H⁺ 542 and 544.

The 1-(3-hydroxypropyl)-4-isobutyrylpiperazine used as a starting material was prepared as follows :-

- Isobutyryl chloride (1.3 ml) was added dropwise to a stirred mixture of
- 25 1-benzylpiperazine (2 g), triethylamine (1.74 ml) and methylene chloride (30 ml) which was cooled to 0°C. The reaction mixture was allowed to warm to ambient temperature and stirred for 1 hour. The mixture was partitioned between methylene chloride and water. The organic phase was washed with water and with brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 3:2 mixture of
- 30 methylene chloride and ethyl acetate as eluent. There was thus obtained 1-benzyl-4-isobutyrylpiperazine (2.6 g) as an oil; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 1.15 (d, 6H), 2.45 (m, 4H), 2.8 (m, 1H), 3.5 (m, 4H), 3.65 (m, 2H), 7.3 (m, 5H); Mass Spectrum: M+H⁺ 247.

The material so obtained was treated according to the procedures described in the last two paragraphs of the portion of Note [32] immediately above that is concerned with the preparation of starting materials. There was thus obtained 1-(3-hydroxypropyl)-4-isobutyrylpiperazine as a liquid (1.7 g); NMR Spectrum: (CDCl₃) 1.1 (d, 6H), 1.7 (m, 2H), 5 2.45 (m, 4H), 2.6 (t, 2H), 2.75 (m, 1H), 3.5 (m, 2H), 3.6 (m, 2H), 3.8 (t, 2H), 4.7 (br s, 1H); Mass Spectrum: M+H⁺ 215.

Example 9

7-(2-homopiperidin-1-ylethoxy)-4-(2,3-methylenedioxyanilino)-6-methoxyquinazoline

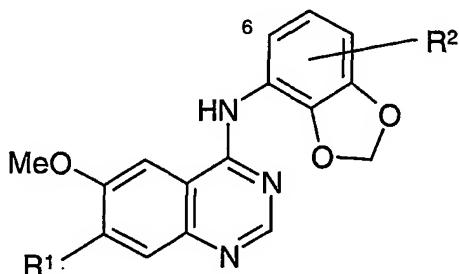
10 A mixture of 7-(2-bromoethoxy)-4-(2,3-methylenedioxyanilino)-6-methoxyquinazoline (0.48 g) homopiperidine (0.322 ml), sodium iodide (0.002 g), DMF (5 ml) and acetonitrile (6 ml) was stirred and heated to 45°C for 5 hours. The mixture was evaporated and the residue was partitioned between methylene chloride and water. The organic phase was washed with brine, dried over magnesium sulphate and evaporated. The 15 residue was purified by column chromatography on silica using a 19:1 mixture of methylene chloride and a saturated methanolic ammonia solution as eluent. The material so obtained was triturated under diethyl ether to give the title compound as a solid (0.4 g); NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 1.65 (m, 4H), 1.9 (m, 4H), 3.35 (m, 2H), 3.55 (m, 2H), 3.7 (m, 2H), 4.0 (s, 3H), 4.6 (m, 2H), 6.1 (s, 2H), 7.0 (m, 3H), 7.45 (s, 1H), 8.15 (s, 1H), 8.9 20 (s, 1H); Mass Spectrum: M+H⁺ 437.

The 7-(2-bromoethoxy)-4-(2,3-methylenedioxyanilino)-6-methoxyquinazoline used as a starting material was prepared as follows :-

1,1'-(Azodicarbonyl)dipiperidine (6 g) was added to a stirred mixture of 7-hydroxy-4-(2,3-methylenedioxyanilino)-6-methoxyquinazoline (3 g), 2-bromoethanol (1 ml), 25 tributylphosphine (5.9 ml) and chloroform (300 ml) which was heated to 40°C. The mixture was heated to 40°C for 10 minutes and then stirred at ambient temperature for 2 hours. The mixture was evaporated and the residue was purified by column chromatography on silica using a 11:9 mixture of methylene chloride and acetonitrile as eluent. There was thus obtained 7-(2-bromoethoxy)-4-(2,3-methylenedioxyanilino)-6-methoxyquinazoline (1.8 g); 30 NMR Spectrum: (DMSO_d₆) 3.9 (t, 2H), 3.95 (s, 3H), 4.55 (t, 2H), 6.05 (s, 2H), 6.9 (m, 3H), 7.2 (s, 1H), 7.9 (s, 1H), 8.4 (s, 1H), 9.65 (br s, 1H).

Example 10

Using an analogous procedure to that described in Example 9, the appropriate 7-haloalkoxyquinazoline was reacted with the appropriate amine to give the compounds described in Table III. Unless otherwise stated, each compound described in Table III was 5 obtained as the free base.

Table III

Compound No. & Note	R ¹	R ²
[1]	2-pyrrolidin-1-yethoxy	hydrogen
[2]	2-piperidinoethoxy	hydrogen
[3]	3-homopiperidin-1-ylpropoxy	hydrogen
[4]	3-(<i>cis</i> -3,5-dimethylpiperazin-1-yl)propoxy	6-chloro
[5]	3-(4-hydroxypiperidin-1-yl)propoxy	6-chloro
[6]	3-[N,N-di-(2-hydroxyethyl)amino]propoxy	6-chloro

10 Notes

- [1] 7-(2-Bromoethoxy)-4-(2,3-methylenedioxyanilino)-6-methoxyquinazoline was used as a starting material, DMF was used as the sole reaction solvent and the reaction mixture was warmed to 27°C for 4 hours. The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 1.9 (m, 2H), 2.1 (m, 2H), 3.2 (m, 2H), 3.7 (m, 2H), 3.75 (m, 2H), 4.0 (s, 3H), 4.55 (m, 2H), 6.1 (s, 2H), 7.0 (m, 3H), 7.45 (s, 1H), 8.15 (s, 1H), 8.9 (d, 1H); Mass Spectrum: M-H⁺ 407.
- [2] 7-(2-Bromoethoxy)-4-(2,3-methylenedioxyanilino)-6-methoxyquinazoline was used as a starting material, DMF was used as the sole reaction solvent and the reaction mixture was warmed to 30°C for 3.5 hours. The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 1.4 (m, 1H), 1.7 (m, 3H), 1.9 (m, 2H), 3.1 (t, 2H), 3.6

(m, 2H), 3.65 (m, 2H), 4.05 (s, 3H), 4.6 (t, 2H), 6.1 (s, 2H), 7.0 (m, 3H), 7.4 (s, 1H), 8.15 (s, 1H), 8.9 (s, 1H); Mass Spectrum: M+H⁺ 423.

[3] The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 1.6 (m, 4H), 1.8 (m, 4H), 2.3 (m, 2H), 3.2 (m, 2H), 3.3 (m, 2H), 3.45 (m, 2H), 4.0 5 (s, 3H), 4.3 (t, 2H), 6.1 (s, 2H), 7.0 (m, 3H), 7.4 (s, 1H), 8.1 (s, 1H), 8.9 (s, 1H); Mass Spectrum: M+H⁺ 451.

The 7-(3-chloropropoxy)-4-(2,3-methylenedioxyanilino)-6-methoxyquinazoline used as a starting material was prepared as follows :-

A mixture of 7-hydroxy-4-(2,3-methylenedioxyanilino)-6-methoxyquinazoline (2 g) 10 and DMF (40 ml) was warmed until the starting material was completely dissolved. The solution was cooled to ambient temperature and 3-chloropropyl bromide (0.826 ml), tetrabutylammonium iodide (0.237 g) and caesium carbonate (4.2 g) were added in turn. The resultant mixture was stirred at ambient temperature for 20 hours. Water was added and the mixture was extracted with ethyl acetate (2x). The combined organic phases were washed 15 with water and with brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 24:1 mixture of methylene chloride and methanol as eluent. There was thus obtained 7-(3-chloropropoxy)-4-(2,3-methylenedioxyanilino)-6-methoxyquinazoline (1.8 g); NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 2.3 (m, 2H), 3.85 (t, 2H), 4.0 (s, 3H), 4.35 (t, 2H), 6.1 (s, 2H), 7.0 (m, 3H), 7.35 (s, 20 1H), 8.1 (s, 1H), 8.85 (s, 1H); Mass Spectrum: M+H⁺ 388 and 390.

[4] Acetonitrile was used as the sole reaction solvent and the reaction mixture was warmed to 60°C for 5 hours. The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 1.29 (s, 3H), 1.31 (s, 3H), 2.35 (m, 2H), 3.0 (m, 2H), 3.4 (m, 2H), 3.65 (m, 2H), 3.85 (m, 2H), 4.0 (s, 3H), 4.35 (m, 2H), 6.15 (s, 2H), 7.05 (d, 1H), 25 7.15 (d, 1H), 7.4 (s, 1H), 8.15 (s, 1H), 8.9 (s, 1H); Mass Spectrum: M-H⁻ 498 and 500.

The 7-(3-bromopropoxy)-4-(6-chloro-2,3-methylenedioxyanilino)-6-methoxyquinazoline used as a starting material was prepared as follows :-

1,1'-(Azodicarbonyl)dipiperidine (0.725 g) was added to a stirred mixture of 4-(6-chloro-2,3-methylenedioxyanilino)-7-hydroxy-6-methoxyquinazoline (0.5 g), 30 3-bromopropanol (0.234 ml), tributylphosphine (0.715 ml), methylene chloride (50 ml) and THF (20 ml) and the reaction mixture was stirred at ambient temperature for 1 hour. Second portions of tributylphosphine (0.357 ml) and 1,1'-(azodicarbonyl)dipiperidine (0.362 g) were added and the reaction mixture was stirred for another 2 hours. The resultant mixture was

evaporated and the residue was purified by column chromatography on silica using a 7:3 mixture of methylene chloride and acetonitrile as eluent. There was thus obtained 7-(3-bromopropoxy)-4-(6-chloro-2,3-methylenedioxyanilino)-6-methoxyquinazoline as a solid (0.3 g); NMR Spectrum: (DMSO_d₆) 2.35 (m, 2H), 3.7 (t, 2H), 3.95 (s, 3H), 4.25 (t, 2H), 6.1 (s, 2H), 6.95 (d, 1H), 7.05 (d, 1H), 7.2 (s, 1H), 7.85 (s, 1H), 8.3 (s, 1H), 9.5 (s, 1H); Mass Spectrum: M+H⁺ 466.

[5] The reaction mixture was heated to reflux for 16 hours. The product gave the following characterising data; NMR Spectrum: (DMSO_d₆) 1.4 (m, 2H), 1.75 (m, 2H), 1.95 (m, 2H), 2.0 (m, 2H), 2.4 (t, 2H), 2.75 (m, 2H), 3.5 (m, 1H), 3.95 (s, 3H), 4.2 (t, 2H), 4.55 (s, 1H), 6.1 (s, 2H), 6.95 (d, 1H), 7.1 (d, 1H), 7.2 (s, 1H), 7.85 (s, 1H), 8.35 (s, 1H), 9.5 (s, 1H); Mass Spectrum: M+H⁺ 487.

The 4-(6-chloro-2,3-methylenedioxyanilino)-7-(3-chloropropoxy)-6-methoxyquinazoline used as a starting material was prepared as follows :-

A mixture of 4-(6-chloro-2,3-methylenedioxyanilino)-7-hydroxy-6-methoxyquinazoline (1.5 g), 3 chloropropyl bromide (0.54 ml), potassium carbonate (1.5 g) and DMF (20 ml) was stirred at ambient temperature for 16 hours. The mixture was partitioned between ethyl acetate and water. The organic phase was washed with water and with brine, dried over magnesium sulphate and evaporated. The residue was triturated under diethyl ether and the resultant solid was isolated, washed with diethyl ether and dried under vacuum. There was thus obtained 4-(6-chloro-2,3-methylenedioxyanilino)-7-(3-chloropropoxy)-6-methoxyquinazoline (1.34 g); NMR Spectrum: (DMSO_d₆) 2.25 (m, 2H), 3.85 (t, 2H), 3.95 (t, 3H), 4.3 (t, 2H), 6.1 (s, 2H), 6.95 (d, 1H), 7.05 (d, 1H), 7.15 (s, 1H), 7.85 (s, 1H), 8.35 (s, 1H), 9.5 (br s, 1H).

[6] 4-(6-Chloro-2,3-methylenedioxyanilino)-7-(3-chloropropoxy)-6-methoxyquinazoline was used as a starting material and the reaction mixture was heated to reflux for 16 hours. The product gave the following characterising data; NMR Spectrum: (DMSO_d₆) 1.9 (m, 2H), 2.7 (m, 2H), 3.35-3.5 (m, 8H), 3.95 (s, 3H), 4.2 (t, 2H), 4.35 (t, 2H), 6.1 (s, 2H), 6.95 (d, 1H), 7.1 (d, 1H), 7.2 (s, 1H), 7.85 (s, 1H), 8.3 (s, 1H), 9.5 (s, 1H); Mass Spectrum: M+H⁺ 491.

Example 11**4-(6-chloro-2,3-methylenedioxyanilino)-6-methoxy-7-(3-piperazin-1-ylpropoxy)quinazoline dihydrochloride salt**

A mixture of 7-[3-(4-*tert*-butoxycarbonylpiperazin-1-yl)propoxy]-4-(6-chloro-2,3-methylenedioxyanilino)-6-methoxyquinazoline (0.286 g), trifluoroacetic acid (0.5 ml) and methylene chloride (6 ml) was stirred at ambient temperature for 3 hours. The solvent was evaporated and the residue was partitioned between methylene chloride and a saturated aqueous sodium bicarbonate solution. The organic phase was washed with water and with brine, dried over magnesium sulphate and evaporated. The material so obtained was triturated under a 6M solution of hydrogen chloride in diethyl ether. There was thus obtained the title compound (0.205 g); NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 2.35 (m, 2H), 3.2-3.9 (m, 10H), 4.0 (s, 3H), 4.35 (m, 2H), 6.12 (s, 2H), 7.0 (s, 1H), 7.1 (s, 1H), 7.38 (s, 1H), 8.15 (s, 1H), 8.85 (s, 1H); Mass Spectrum: M+H⁺ 472 and 474

Example 12**4-(6-chloro-2,3-methylenedioxyanilino)-7-[3-(4-cyanomethylpiperazin-1-yl)propoxy]-6-methoxyquinazoline**

A mixture of 4-(6-chloro-2,3-methylenedioxyanilino)-6-methoxy-7-(3-piperazin-1-ylpropoxy)quinazoline (0.19 g), 2-chloroacetonitrile (0.038 ml), potassium iodide (0.020 g), potassium carbonate (0.139 g) and DMF (2.5 ml) was stirred at ambient temperature for 16 hours. The reaction mixture was partitioned between ethyl acetate and water. The organic phase was washed with water and with brine, dried over magnesium sulphate and evaporated. The crude product was purified by column chromatography on silica using a 93:7 mixture of methylene chloride and methanol as eluent. There was thus obtained the title compound (0.13 g) as a solid; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 2.3 (m, 2H), 2.6 (m, 2H), 3.05 (m, 2H), 3.15 (m, 2H), 3.35 (m, 2H), 3.65 (m, 2H), 3.9 (s, 2H), 4.05 (s, 3H), 4.35 (m, 2H), 6.15 (s, 2H), 7.05 (d, 1H), 7.15 (d, 1H), 7.4 (s, 1H), 8.15 (s, 1H), 8.9 (s, 1H); Mass Spectrum: [M-H]⁻ 509 and 511; Elemental Analysis: Found C, 58.41; H, 5.62; N, 15.93; C₂₅H₂₇ClN₆O₄ 0.2H₂O requires C, 58.35; H, 5.37; N, 16.33%.

Example 13**6-methoxy-4-(2,3-methylenedioxyanilino)-7-(3-piperazin-1-ylpropoxy)quinazoline dihydrochloride salt**

Using an analogous procedure to that described in Example 11,

- 5 7-[3-(4-*tert*-butoxycarbonylpiperazin-1-yl)propoxy]-6-methoxy-4-(2,3-methylenedioxyanilino)quinazoline was reacted with trifluoroacetic acid to give the title compound; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 2.3-2.4 (m, 2H), 3.2-3.95 (m, 10H), 4.05 (s, 3H), 4.38 (m, 2H), 6.1 (s, 2H), 7.0 (s, 3H), 7.4 (s, 1H), 8.2 (s, 1H), 8.9 (s, 1H); Mass Spectrum: M+H⁺ 438.

10

Example 14**7-[3-(4-cyanomethylpiperazin-1-yl)propoxy]-6-methoxy-4-(2,3-methylenedioxyanilino)quinazoline**

Using an analogous procedure to that described in Example 12, 6-methoxy-

- 15 4-(2,3-methylenedioxyanilino)-7-(3-piperazin-1-ylpropoxy)quinazoline was reacted with 2-chloroacetonitrile to give the title compound as a solid; NMR Spectrum: (DMSO_d₆) 2.1 (m, 2H), 2.45-2.7 (m, 11H), 3.5 (s, 2H), 4.0 (s, 3H), 4.25 (t, 2H), 6.0 (s, 2H), 6.7 (d, 1H), 6.9 (t, 1H), 7.0 (m, 2H), 7.75 (d, 1H), 8.7 (s, 1H); Mass Spectrum: M+H⁺ 477.

20 **Example 15****4-(6-bromo-2,3-methylenedioxyanilino)-6-methoxy-7-(3-piperidinopropoxy)quinazoline**

Sodium hexamethyldisilazane (1M solution in THF; 0.626 ml) was added to a solution of 6-bromo-2,3-methylenedioxyaniline (0.135 g) in DMF (2 ml) and the mixture was stirred at ambient temperature for 30 minutes. A solution of 4-chloro-6-methoxy-

- 25 7-(3-piperidinopropoxy)quinazoline (0.1 g) in DMF (3.5 ml) was added and the resultant mixture was stirred at ambient temperature for 3 hours. The reaction mixture was diluted with water and extracted with ethyl acetate (2x). The organic phase was washed with water and with brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using an 80:17:3 mixture of methylene chloride, methanol 30 and a saturated methanolic ammonia solution as eluent. There was thus obtained the title compound as a solid (0.045 g); NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 1.4 (m, 1H), 1.7 (m, 3H), 1.85 (m, 2H), 2.3 (m, 2H), 2.95 (m, 2H), 3.25 (m, 2H), 3.55 (m, 2H), 4.05 (s, 3H), 4.3 (m, 2H), 6.15 (s, 2H), 7.05 (d, 1H), 7.3 (d, 1H), 7.4 (s, 1H), 8.15 (s, 1H), 8.9 (s, 1H); Mass

Spectrum: M+H⁺ 515 and 517; Elemental Analysis: Found C, 55.74; H, 5.30; N, 10.76;
C₂₄H₂₇BrN₄O₄ requires C, 55.93; H, 5.28; N, 10.87%.

Example 16

5 4-(6-bromo-2,3-methylenedioxyanilino)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline

Using an analogous procedure to that described in Example 15, 4-chloro-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline was reacted with 6-bromo-2,3-methylenedioxyaniline to give the title compound as a solid; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 2.3 (m, 2H), 2.95 (s, 3H), 3.2-3.9 (br s, 8H), 3.4 (m, 2H), 4.0 (s, 3H), 4.35 (m, 2H), 6.15 (s, 2H), 7.05 (d, 1H), 7.3 (d, 1H), 7.4 (s, 1H), 8.15 (s, 1H), 8.9 (s, 1H); Mass Spectrum: M+H⁺ 530 and 532; Elemental Analysis: Found C, 54.25; H, 5.54; N, 12.8%; C₂₄H₂₈BrN₅O₄ requires C, 54.35; H, 5.32; N, 13.2%.

15 Example 17

7-[2-(4-hydroxypiperidin-4-yl)ethoxy]-6-methoxy-4-(2,3-methylenedioxyanilino)quinazoline

A mixture of 7-[2-(N-tert-butoxycarbonyl-4-hydroxypiperidin-4-yl)ethoxy]-6-methoxy-4-(2,3-methylenedioxyanilino)quinazoline (0.067 g), trifluoroacetic acid (0.5 ml) 20 and methylene chloride (3 ml) was stirred at ambient temperature for 1 hour. The solvent was evaporated and the residue was partitioned between methylene chloride and a saturated aqueous sodium bicarbonate solution. The organic phase was washed with brine, dried over magnesium sulphate and evaporated. There was thus obtained the title compound (0.015 g); NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 1.75 (m, 4H), 2.05 (t, 2H), 3.1 (m, 4H), 4.0 (s, 3H), 4.35 (t, 2H), 6.1 (s, 2H), 6.95 (m, 3H), 7.4 (s, 1H), 8.1 (s, 1H), 8.85 (s, 1H); Mass Spectrum: M+H⁺ 439.

Example 18

7-[2-(4-hydroxy-N-methylpiperidin-4-yl)ethoxy]-6-methoxy-

30 4-(2,3-methylenedioxyanilino)quinazoline

A mixture of 7-[2-(4-hydroxypiperidin-4-yl)ethoxy]-6-methoxy-4-(2,3-methylenedioxyanilino)quinazoline (0.065 g), formaldehyde (40% aqueous solution; 0.2 ml) and formic acid (2 ml) was stirred and heated to 100°C for 1.5 hours. The mixture

was basified to pH9.5 by the addition of 2N aqueous sodium hydroxide solution and extracted with ethyl acetate. The organic phase was washed with water and with brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using an 80:17:3 mixture of methylene chloride, methanol and a saturated methanolic 5 ammonia solution as eluent. There was thus obtained the title compound as a solid (0.021 g); NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 1.8 (m, 4H), 2.05 (m, 2H), 2.8 (s, 3H), 3.15 (m, 2H), 3.3 (m, 2H), 4 (s, 3H), 4.35 (m, 2H), 6.05 (s, 2H), 6.95 (m, 3H), 7.4 (s, 1H), 8.1 (s, 1H), 8.85 (s, 1H); Mass Spectrum: M+H⁺ 453.

10 **Example 19**

4-(6-chloro-2,3-methylenedioxyanilino)-6-methoxy-7-(piperidin-4-ylmethoxy)quinazoline dihydrochloride salt

Using an analogous procedure to that described in Example 11,
7-(N-tert-butoxycarbonylpiperidin-4-ylmethoxy)-4-(6-chloro-2,3-methylenedioxyanilino)-15 6-methoxyquinazoline was reacted with trifluoroacetic acid. The material so obtained was triturated under a 6M solution of hydrogen chloride in diethyl ether. There was thus obtained the title compound; NMR Spectrum: (DMSO_d₆) 1.5-1.65 (m, 2H), 2.0 (d, 2H), 2.2 (m, 1H), 2.95 (m, 2H), 3.2-3.4 (m, 2H), 4.02 (s, 3H), 4.12 (d, 2H), 6.15 (s, 2H), 7.05 (d, 1H), 7.15 (d, 1H), 7.42 (s, 1H), 8.22 (s, 1H), 8.8 (s, 1H); Mass Spectrum: M+H⁺ 443 and 445.

20

Example 20

4-(6-chloro-2,3-methylenedioxyanilino)-7-(N-cyanomethylpiperidin-4-ylmethoxy)-6-methoxyquinazoline

Using an analogous procedure to that described in Example 12, 4-(6-chloro-2,3-methylenedioxyanilino)-6-methoxy-7-(piperidin-4-ylmethoxy)quinazoline was reacted with 2-chloroacetonitrile to give the title compound as a solid; NMR Spectrum: (DMSO_d₆) 1.65 (m, 2H), 2.1 (m, 2H), 2.2 (m, 1H), 3.15 (m, 2H), 3.6 (m, 2H), 4.05 (s, 3H), 4.15 (m, 2H), 4.55 (s, 2H), 6.15 (s, 2H), 7.05 (d, 1H), 7.15 (d, 1H), 7.4 (s, 1H), 8.15 (s, 1H), 8.9 (s, 1H); Mass Spectrum: M-H⁻ 480 and 482.

30

Example 21**7-(2-hydroxy-3-morpholinopropoxy)-6-methoxy-
4-(2,3-methylenedioxyanilino)quinazoline dihydrochloride salt**

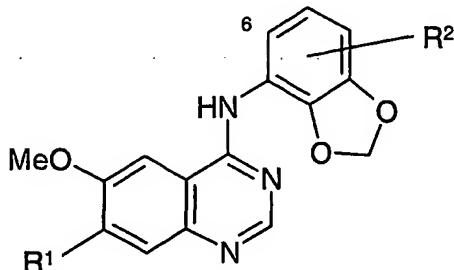
A mixture of 7-(2-acetoxy-3-morpholinopropoxy)-6-methoxy-

- 5 4-(2,3-methylenedioxyanilino)quinazoline dihydrochloride (0.104 g) and a saturated methanolic ammonia solution (3 ml) was stirred at ambient temperature for 16 hours. The mixture was evaporated and the residue was purified by column chromatography on silica (Isolute ammonia-treated silica from International Sorbent Technology Limited, catalogue reference 9470-0100) using a 19:1 mixture of methylene chloride and methanol as eluent.
- 10 The material so obtained was dissolved in methylene chloride (3 ml) and a 6M solution of hydrogen chloride in isopropanol (0.3ml) was added with stirring. Diethyl ether (10 ml) was added and the resultant precipitate was isolated, washed with diethyl ether and dried under vacuum. There was thus obtained the title compound (0.095 g); NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 3.15-3.45 (m, 4H), 3.54 (d, 2H), 3.74-3.91 (d, 2H), 3.97 (d, 2H), 4.02 (s, 3H),
- 15 4.24 (d, 2H), 4.49-4.58 (m, 1H), 6.08 (s, 2H), 6.96-7.04 (m, 3H), 7.47 (s, 1H), 8.23 (s, 1H), 8.88 (s, 1H); Mass Spectrum: M+H⁺ 455.

Example 22

Using an analogous procedure to that described in Example 21, the appropriate

- 20 7-(2-acetoxypropoxy)quinazoline was cleaved to give the compounds described in Table IV. Unless otherwise stated, each compound described in Table IV was obtained as a dihydrochloride salt.

Table IV

25

Compound No. & Note	R ¹	R ²
[1]	2-hydroxy-3-pyrrolidin-1-ylpropoxy	hydrogen

[2]	2-hydroxy-3-piperidinopropoxy	hydrogen
[3]	3-(4-cyanomethylpiperazin-1-yl)-2-hydroxypropoxy	hydrogen
[4]	2-hydroxy-3-(N-isopropyl-N-methylamino)propoxy	hydrogen

Notes

- [1] The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 1.85-1.98 (m, 2H), 1.99-2.1 (m, 2H), 3.07-3.2 (m, 2H), 3.33-3.42 (m, 2H), 5 3.57-3.68 (m, 2H), 4.02 (s, 3H), 4.22 (d, 2H), 4.34-4.43 (m, 1H), 6.08 (s, 2H), 6.94-7.04 (m, 3H), 7.45 (s, 1H), 8.22 (s, 1H), 8.87 (s, 1H); Mass Spectrum: M+H⁺ 439.
- [2] The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 1.36-1.51 (m, 1H), 1.65-1.78 (m, 2H), 1.79-1.92 (m, 3H), 2.93-3.11 (m, 2H), 3.2-3.74 (m, 2H), 3.54 (t, 2H), 4.02 (s, 3H), 4.24 (d, 2H), 4.46-4.54 (m, 1H), 6.08 (s, 2H), 10 6.95-7.03 (m, 3H), 7.44 (s, 1H), 8.2 (s, 1H), 8.88 (s, 1H); Mass Spectrum: M+H⁺ 453.
- [3] The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 2.54-3.12 (m, 4H), 3.13-3.48 (m, 3H), 3.55-3.73 (m, 2H), 3.89 (s, 3H), 4.03 (s, 3H), 4.22-4.3 (m, 2H), 4.46-4.59 (m, 1H), 6.08 (s, 2H), 7.95-7.03 (m, 3H), 7.49 (s, 1H), 8.27 (s, 1H), 8.87 (s, 1H); Mass Spectrum: M+H⁺ 493.
- 15 [4] The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 1.2-1.36 (m, 6H), 2.78 (d, 3H), 3.04-3.71 (m, 3H), 4.03 (s, 3H), 4.24 (d, 2H), 4.41-4.55 (m, 1H), 6.05 (s, 2H), 5.88-6.06 (m, 3H), 7.48 (d, 1H), 8.36 (s, 1H), 8.82 (s, 1H), 9.5-10.1 (m, 1H), 11.65 (s, 1H); Mass Spectrum: M+H⁺ 441.

20 Example 23

**7-[(2R)-2-hydroxy-3-pyrrolidin-1-ylpropoxy]-6-methoxy-
4-(2,3-methylenedioxyanilino)quinazoline dihydrochloride salt**

A mixture of pyrrolidine (0.016 ml), 7-[(2R)-2,3-epoxypropoxy]-6-methoxy-4-(2,3-methylenedioxyanilino)quinazoline (0.03 g), chloroform (0.5 ml) and ethanol (0.5 ml) was stirred and heated to 40°C for 7 hours. The mixture was evaporated and the residue was dissolved in methylene chloride (4 ml). A polystyrene isocyanate resin (prepared according to *J. Amer. Chem. Soc.*, 1997, 119, 4882; loading: 1 mmol/g; 0.3 g) was added and the mixture was shaken at ambient temperature for 1.5 hours. The resin was removed by filtration and washed with methylene chloride. The filtrate was evaporated and the crude product so

obtained was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and a saturated methanolic ammonia solution as eluent. The material so obtained was dissolved in a 9:1 mixture of methylene chloride and methanol (3 ml) and a 2.2M solution of hydrogen chloride in diethyl ether (1 ml) was added. The precipitate was isolated and dried under vacuum. There was thus obtained the title compound (0.026 g);

NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 1.85-2.15 (m, 4H), 3.06-3.25 (m, 2H), 3.31-3.47 (m, 2H), 3.6-3.74 (m, 2H), 4.04 (s, 3H), 4.8 (d, 2H), 4.38-4.46 (m, 1H), 6.1 (s, 2H), 6.94-7.05 (m, 3H), 7.49 (s, 1H), 8.27 (s, 1H), 8.88 (s, 1H); Mass Spectrum: M+H⁺ 439.

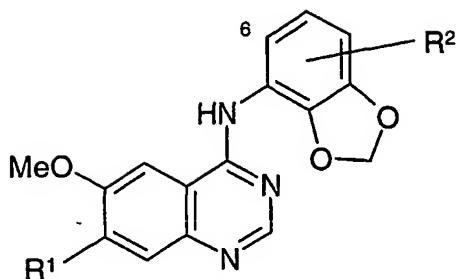
The 7-[(2R)-2,3-epoxypropoxy]-6-methoxy-4-(2,3-methylenedioxyanilino)quinazoline used as a starting material was prepared as follows :-

(2R)-(-)-Glycidyl tosylate (3.2 g) was added to a mixture of 7-hydroxy-4-(2,3-methylenedioxyanilino)-6-methoxyquinazoline (4 g), potassium carbonate (8.8 g) and DMF (80 ml) and the mixture was stirred at ambient temperature for 16 hours. The resultant precipitate was isolated and the filtrate was evaporated to give a first batch of the reaction product. The precipitate was triturated under a mixture of ethyl acetate and a 5% aqueous ammonium hydroxide solution. The mixture was filtered and the filtrate was washed with water and with brine, dried over magnesium sulphate and evaporated to give a further batch of the reaction product. The batches of product were combined and purified by column chromatography on silica using a 12:7:1 mixture of methylene chloride, ethyl acetate and methanol as eluent. There was thus obtained 7-[(2R)-2,3-epoxypropoxy]-6-methoxy-4-(2,3-methylenedioxyanilino)quinazoline as a solid (3.11 g); NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 2.85 (m, 1H), 2.95 (m, 1H), 3.5 (m, 1H), 4.0 (s, 3H), 4.1 (m, 1H), 4.65 (m, 1H), 6.1 (s, 2H), 7.0 (m, 3H), 7.35 (s, 1H), 8.1 (s, 1H), 8.85 (s, 1H).

25 Example 24

Using an analogous procedure to that described in Example 22, 7-[(2R)-2,3-epoxypropoxy]-6-methoxy-4-(2,3-methylenedioxyanilino)quinazoline was reacted with the appropriate amine to give the compounds described in Table V. Unless otherwise stated, each compound described in Table V was obtained as a dihydrochloride salt.

Table V



Compound No. & Note	R ¹	R ²
[1]	(2R)-2-hydroxy-3-piperidinopropoxy	hydrogen
[2]	(2R)-3-homopiperidin-1-yl-2-hydroxypropoxy	hydrogen
[3]	(2R)-2-hydroxy-3-(<u>N</u> -isopropyl- <u>N</u> -methylamino)propoxy	hydrogen
[4]	(2R)-2-hydroxy-3-(<u>N</u> -isobutyl- <u>N</u> -methylamino)propoxy	hydrogen
[5]	3-[(2S)-2-(<u>N,N</u> -dimethylcarbamoyl)pyrrolidin-1-yl]- (2R)-2-hydroxypropoxy	hydrogen
[6]	(2R)-3-(<u>N</u> -allyl- <u>N</u> -cyclopentylamino)-2-hydroxypropoxy	hydrogen
[7]	(2R)-3-(<u>N</u> -allyl- <u>N</u> -methylamino)-2-hydroxypropoxy	hydrogen
[8]	(2R)-2-hydroxy-3-pyrrolidin-1-ylpropoxy	6-chloro
[9]	(2R)-2-hydroxy-3-piperidinopropoxy	6-chloro
[10]	(2R)-3-homopiperidin-1-yl-2-hydroxypropoxy	6-chloro
[11]	(2R)-2-hydroxy-3-(<u>N</u> -isopropyl- <u>N</u> -methylamino)propoxy	6-chloro
[12]	(2R)-2-hydroxy-3-(<u>N</u> -isobutyl- <u>N</u> -methylamino)propoxy	6-chloro
[13]	3-[(2S)-2-(<u>N,N</u> -dimethylcarbamoyl)pyrrolidin-1-yl]- (2R)-2-hydroxypropoxy	6-chloro
[14]	(2R)-3-(<u>N</u> -allyl- <u>N</u> -methylamino)-2-hydroxypropoxy	6-chloro

5 Notes

- [1] The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 1.35-1.5 (m, 1H), 1.65-1.94 (m, 5H), 2.93-3.13 (m, 2H), 3.2-3.4 (m, 2H), 3.49-3.61 (m, 2H), 4.03 (s, 3H), 4.24 (d, 2H), 4.47-4.57 (m, 1H), 6.08 (s, 2H), 6.94-7.05 (m, 3H), 7.47 (s, 1H), 8.24 (s, 1H), 8.88 (s, 1H); Mass Spectrum: M-H⁺ 451.

- [2] The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 1.55-1.75 (m, 4H), 1.76-1.96 (m, 4H), 3.2-3.34 (m, 3H), 3.38-3.57 (m, 3H), 4.03 (s, 3H), 4.24 (d, 2H), 4.42-4.52 (m, 1H), 6.09 (s, 2H), 6.94-7.04 (m, 3H), 7.45 (s, 1H), 8.21 (s, 1H), 8.88 (s, 1H); Mass Spectrum: M+H⁺ 467.
- 5 [3] The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 1.21-1.39 (m, 6H), 2.81 (s, 3H), 3.08-3.77 (m, 3H), 4.02 (s, 3H), 4.26 (d, 2H), 4.39-4.53 (m, 1H), 6.08 (s, 2H), 6.92-7.05 (m, 3H), 7.46 (s, 1H), 8.22 (s, 1H), 8.83 (s, 1H); Mass Spectrum: M-H⁻ 439.
- [4] The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 0.91-1.1 (m, 6H), 2.05-2.22 (s, 1H), 2.91 (br s, 3H), 2.92-3.04 (m, 1H), 3.08-3.48 (m, 3H), 4.03 (s, 3H), 4.17-4.34 (m, 2H), 4.45-4.59 (m, 1H), 6.08 (s, 2H), 6.92-7.06 (m, 3H), 7.49 (s, 1H), 8.28 (br s, 1H), 8.87 (s, 1H); Mass Spectrum: M+H⁺ 455.
- 10 [5] The amine starting material was N,N-dimethyl-L-prolinamide. The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 1.78-2.0 (m, 2H), 2.09-2.2 (m, 1H), 2.52-2.63 (m, 1H), 2.95 (s, 3H), 3.02 (m, 3H), 3.23-3.36 (m, 2H), 3.51 (m, 1H), 3.86-3.96 (m, 1H), 4.03 (s, 3H), 4.16-4.3 (m, 2H), 4.39-4.48 (m, 1H), 4.85 (m, 1H), 6.09 (s, 2H), 6.93-7.06 (m, 3H), 7.44 (s, 1H), 8.23 (s, 1H), 8.88 (s, 1H); Mass Spectrum: M+H⁺ 510.
- 15 [6] The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 1.5-2.16 (m, 8H), 3.25-3.44 (m, 2H), 3.65-4.02 (m, 2H), 3.92 (d, 1H), 4.03 (s, 3H), 4.19-4.33 (m, 2H), 4.42-4.57 (m, 1H), 5.55-5.73 (m, 2H), 6.02-6.17 (m, 3H), 6.96-7.03 (m, 3H), 7.41 (s, 1H), 8.18 (s, 1H), 8.89 (s, 1H); Mass Spectrum: M+H⁺ 493.
- 20 [7] The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 2.86 (br s, 3H), 3.19-3.46 (m, 2H), 3.76-3.98 (m, 2H), 4.03 (s, 3H), 4.25 (d, 2H), 4.42-4.53 (m, 1H), 5.52-5.65 (m, 2H), 5.94-6.06 (m, 1H), 6.08 (s, 2H), 6.94-7.05 (m, 3H), 7.43 (br s, 1H), 8.18 (s, 1H), 8.89 (s, 1H); Mass Spectrum: M-H⁻ 437.
- 25 [8] The product gave the following characterising data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 1.8-1.99 (m, 2H), 2.0-2.11 (m, 2H), 3.08-3.22 (m, 2H), 3.33-3.46 (m, 2H), 3.59-3.71 (m, 2H), 4.03 (s, 3H), 4.25 (d, 2H), 4.36-4.45 (m, 1H), 6.16 (d, 2H), 7.07 (d, 1H), 7.16 (d, 1H), 7.49 (s, 1H), 8.24 (s, 1H), 8.91 (s, 1H); Mass Spectrum: M-H⁻ 471 and 473.

The 4-(6-chloro-2,3-methylenedioxylanilino)-7-[(2R)-2,3-epoxypropoxy]-6-methoxyquinazoline used as a starting material was prepared by the reaction of 4-(6-chloro-2,3-methylenedioxylanilino)-7-hydroxy-6-methoxyquinazoline and (2R)-(--)glycidyl tosylate

using an analogous procedure to that described in the portion of Example 23 that is concerned with the preparation of starting materials. The material so obtained gave the following characterising data; NMR Spectrum: (DMSOd₆ and CF₃CO₂D) 2.85 (m, 1H), 2.95 (t, 1H), 3.45 (m, 1H), 4.05 (s, 3H), 4.65 (m, 1H), 6.15 (s, 2H), 7.05 (d, 1H), 7.15 (d, 1H), 7.35 (s, 1H), 8.15 (s, 1H), 8.9 (s, 1H); Mass Spectrum: M-H⁻ 400 and 402.

- [9] The product gave the following characterising data; NMR Spectrum: (DMSOd₆ and CF₃CO₂D) 1.31-1.52 (m, 1H), 1.65-1.97 (m, 5H), 2.9-3.13 (m, 2H), 3.19-3.42 (m, 2H), 3.47-3.61 (m, 2H), 4.03 (s, 3H), 4.26 (d, 2H), 4.45-4.59 (m, 1H), 6.16 (s, 2H), 7.07 (d, 1H), 7.16 (d, 1H), 7.49 (s, 1H), 8.24 (s, 1H), 8.91 (s, 1H); Mass Spectrum: M-H⁻ 485 and 487.
- [10] [10] The product gave the following characterising data; NMR Spectrum: (DMSOd₆ and CF₃CO₂D) 1.52-1.76 (m, 4H), 1.77-2.02 (m, 4H), 3.15-3.34 (m, 3H), 3.36-3.59 (m, 3H), 4.03 (s, 3H), 4.26 (d, 2H), 4.42-4.57 (m, 1H), 6.52 (s, 2H), 7.06 (d, 1H), 7.16 (d, 1H), 7.53 (s, 1H), 8.29 (s, 1H), 8.9 (s, 1H); Mass Spectrum: M-H⁻ 499 and 501.
- [11] The product gave the following characterising data; NMR Spectrum: (DMSOd₆ and CF₃CO₂D) 1.2-1.4 (m, 6H), 2.81 (s, 3H), 3.07-3.74 (m, 3H), 4.04 (s, 3H), 4.27 (d, 2H), 4.4-4.54 (m, 1H), 6.16 (m, 2H), 7.07 (d, 1H), 7.15 (d, 1H), 7.51 (br s, 1H), 8.28 (br s, 1H), 8.9 (s, 1H); Mass Spectrum: M-H⁻ 473 and 475.
- [12] The product gave the following characterising data; NMR Spectrum: (DMSOd₆ and CF₃CO₂D) 0.91-1.13 (m, 6H), 2.06-2.22 (m, 1H), 2.91 (s, 3H), 2.92-3.04 (m, 1H), 3.06-3.47 (m, 3H), 4.04 (s, 3H), 4.26 (d, 2H), 4.44-4.61 (m, 1H), 6.16 (s, 2H), 7.07 (d, 1H), 7.16 (d, 1H), 7.51 (s, 1H), 8.28 (s, 1H), 8.9 (s, 1H); Mass Spectrum: M-H⁻ 487 and 489.
- [13] The product gave the following characterising data; NMR Spectrum: (DMSOd₆ and CF₃CO₂D) 1.77-2.01 (m, 2H), 2.08-2.22 (m, 1H), 2.53-2.63 (m, 1H), 2.95 (s, 3H), 3.01 (s, 3H), 3.22-3.56 (m, 2H), 3.51 (m, 1H), 3.85-3.96 (m, 1H), 4.03 (s, 3H), 4.17-4.3 (m, 2H), 4.39-4.49 (m, 1H), 4.84 (t, 1H), 6.16 (s, 2H), 7.07 (d, 1H), 7.16 (d, 1H), 7.45 (s, 1H), 8.22 (s, 1H), 8.91 (s, 1H); Mass Spectrum: M-H⁻ 542 and 544.
- [14] The product gave the following characterising data; NMR Spectrum: (DMSOd₆ and CF₃CO₂D) 2.83 (br s, 3H), 3.16-3.44 (m, 2H), 3.73-4.0 (m, 2H), 4.03 (s, 3H), 4.26 (d, 2H), 4.42-4.55 (m, 1H), 5.51-5.64 (m, 2H), 5.91-6.02 (m, 1H), 6.16 (s, 2H), 7.07 (d, 1H), 7.16 (d, 1H), 7.50 (br s, 1H), 8.27 (br s, 1H), 8.9 (s, 1H); Mass Spectrum: M-H⁻ 471 and 473.

Example 25**4-(2,2-difluoro-1,3-benzodioxol-4-ylamino)-6-methoxy-
7-(3-morpholinopropoxy)quinazoline dihydrochloride salt**

Using an analogous procedure to that described in Example 1, except that isopropanol
5 was used in place of pentan-2-ol as the reaction solvent and the reaction mixture was heated to
80°C for 3.5 hours, 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (0.15 g) was
reacted with 2,2-difluoro-1,3-benzodioxol-4-ylamine (0.092 g). The precipitate so obtained
was purified by column chromatography on silica using a 19:1 mixture of methylene chloride
and a saturated methanolic ammonia solution as eluent. The material so obtained was
10 dissolved in methylene chloride and a 6M solution of hydrogen chloride in diethyl ether was
added. The dihydrochloride salt so obtained was isolated and dried to give the title compound
(0.045 g); NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 2.35 (m, 2H), 3.15 (m, 2H), 3.35 (m,
2H), 3.55 (d, 2H), 3.8 (t, 2H), 3.9 (m, 2H), 4.0 (s, 3H), 4.35 (t, 2H), 7.35 (m, 2H), 7.45 (m,
2H), 8.3 (s, 1H), 8.95 (s, 1H); Mass Spectrum: M+H⁺ 475.

15

Example 26**6-methoxy-7-[2-(5-methyl-2-morpholinomethylimidazol-1-yl)ethoxy]-
4-(2,3-methylenedioxyanilino)quinazoline**

Di-tert-butyl azodicarboxylate (0.063 g) was added dropwise to a stirred mixture of
20 7-hydroxy-6-methoxy-4-(2,3-methylenedioxyanilino)quinazoline (0.055 g),
1-(2-hydroxyethyl)-5-methyl-2-morpholinomethylimidazole (0.046 g), triphenylphosphine
(0.072 g) and methylene chloride (1 ml). The reaction mixture was stirred at ambient
temperature for 2 hours. The resultant precipitate was isolated, washed with methylene
chloride and dried under vacuum to give the title compound (0.052 g); NMR Spectrum:
25 (DMSO_d₆ and CF₃CO₂D) 2.55 (s, 3H), 3.1 (br s, 4H), 3.8 (br s, 4H), 4.05 (s, 3H), 4.6 (s, 2H),
4.9 (m, 2H), 6.1 (s, 2H), 7.0 (m, 3H), 7.3 (s, 1H), 7.6 (s, 1H), 8.12 (s, 1H), 8.9 (s, 1H); Mass
Spectrum: M+H⁺ 519.

The 1-(2-hydroxyethyl)-5-methyl-2-morpholinomethylimidazole used as a starting
material was prepared as follows :-

30 A mixture of 4-methyl-1-tritylimidazole (J. Heterocyclic Chem., 1982, 19, 253;
32.5 g), methyl bromoacetate (11.4 ml) and acetone (500 ml) was heated to reflux for 2 hours.
The solvent was removed by evaporation and the residue was dissolved in methanol (100 ml)
and heated to reflux for 45 minutes. The mixture was evaporated and the residue was

triturated under diethyl ether. The resultant precipitate was isolated and stirred at ambient temperature for 1 hour in a mixture of diethyl ether (200 ml) and a saturated methanolic ammonia solution (20 ml). The mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography on silica using a 49:1 mixture of methylene chloride and methanol as eluent. There was thus obtained methyl 2-(5-methylimidazol-1-yl)acetate (6 g); NMR Spectrum: (CDCl₃) 2.16 (s, 3H), 3.78 (s, 3H), 4.61 (s, 3H), 6.8 (s, 1H), 7.42 (s, 1H).

A solution of a portion (1.7 g) of the material so obtained in diethyl ether (20 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (0.76 g) in diethyl ether (70 ml) which was cooled to 0°C. The resultant mixture was stirred at ambient temperature for 1 hour. The mixture was cooled to 0°C and a 6N aqueous sodium hydroxide solution (0.8 ml) and water (2.4 ml) were added dropwise in turn. The mixture was stirred at ambient temperature for 30 minutes and then evaporated. The residue was dissolved in methylene chloride, dried over magnesium sulphate and evaporated to give 1-(2-hydroxyethyl)-5-methylimidazole (1.1 g); NMR Spectrum: (CDCl₃) 2.17 (s, 3H), 3.81 (t, 2H), 3.92 (t, 2H), 6.6 (s, 1H), 7.24 (s, 1H).

Tert-butyldimethylsilyl chloride (9.05 g) was added to a stirred mixture of 1-(2-hydroxyethyl)-5-methylimidazole (6.4 g), imidazole (7.5 g) and methylene chloride (30 ml) which was cooled to 0°C. The reaction mixture was stirred at ambient temperature for 4 hours. The mixture was poured into water. The organic layer was washed with brine, dried over magnesium sulphate and evaporated to give 1-(2-tert-butyldimethylsilyloxyethyl)-5-methylimidazole (11.7 g); NMR Spectrum: (CDCl₃) -0.04 (s, 6H), 0.85 (s, 6H), 2.2 (s, 3H), 3.8 (m, 2H), 3.94 (m, 2H), 6.75 (s, 1H), 7.43 (s, 1H).

The material so obtained was dissolved in THF (400 ml) and the solution was cooled at -60°C. n-Butyllithium (2.5M in hexane, 40 ml) was added dropwise and the mixture was stirred at -50°C for 1 hour. The mixture was cooled to -60°C and DMF (12.5 ml) was added dropwise. The resultant mixture was allowed to warm to ambient temperature and was stirred for 2 hours. Diethyl ether (500 ml) was added and the reaction mixture was poured into a saturated aqueous ammonium chloride solution. The organic layer was separated, washed with brine, dried over magnesium sulphate and evaporated. The material so obtained was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and a saturated methanolic ammonia solution as eluent. There was thus obtained 1-(2-tert-butyldimethylsilyloxyethyl)-2-formyl-5-methylimidazole (11 g); NMR Spectrum:

(CDCl₃) -0.1 (s, 6H), 0.79 (s, 9H), 2.32 (s, 3H), 3.91 (t, 2H), 4.4 (t, 2H), 7.07 (s, 1H), 9.71 (s, 1H).

A portion (0.79 g) of the material so obtained was dissolved in methylene chloride (24 ml) and morpholine (0.263 ml) and acetic acid (0.175 ml) were added. Sodium 5 borohydride triacetate (0.8 g) was added portionwise and the mixture was stirred at ambient temperature for 16 hours. The mixture was evaporated and the residue was purified by column chromatography on silica using a 49:1 mixture of methylene chloride and a saturated methanolic ammonia solution as eluent. There was thus obtained 1-(2-*tert*-butyldimethylsilyloxyethyl)-5-methyl-2-morpholinomethylimidazole (0.5 g); NMR 10 Spectrum: (CDCl₃) 0 (s, 6H), 0.82 (s, 9H), 2.25 (s, 3H), 2.45 (m, 4H), 3.6 (s, 2H), 3.68 (m, 4H), 3.85 (t, 2H), 4.1 (t, 2H), 6.7 (s, 1H).

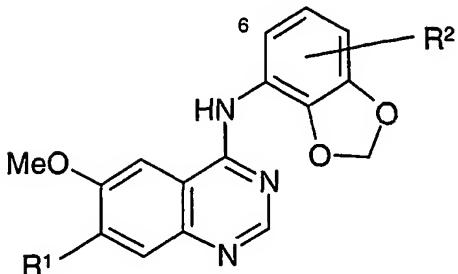
A mixture of the material so obtained, 12N aqueous hydrochloric acid (0.26 ml) and methanol (10 ml) was stirred at ambient temperature for 5 hours. The mixture was evaporated and the residue was triturated under pentane. The resultant solid was isolated and dried under 15 vacuum. The solid was stirred at ambient temperature for 1 hour in a mixture of methylene chloride and a saturated methanolic ammonia solution. The mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography on silica using a 19:1 mixture of methylene chloride and a saturated methanolic ammonia solution as eluent. There was thus obtained 1-(2-hydroxyethyl)-5-methyl-2-morpholinomethylimidazole (0.25 g); 20 NMR Spectrum: (CDCl₃) 2.2 (s, 3H), 2.6 (br s, 4H), 3.58 (s, 2H), 3.7 (m, 4H), 3.85 (t, 2H), 4.1 (t, 2H), 6.5-6.9 (br s, 1H), 6.65 (s, 1H).

Example 27

Using an analogous procedure to that described in Example 26 except that the reaction 25 mixture was stirred at ambient temperature for 16 hours, the appropriate 7-hydroxyquinazoline was reacted with the appropriate alcohol to give the compounds described in Table VI. When each reaction was complete, the reaction mixture was evaporated and the residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and a saturated methanolic ammonia 30 solution as eluent. The product obtained after chromatographic purification was dissolved in diethyl ether and a 6.3M solution of hydrogen chloride in isopropanol was added. The resultant dihydrochloride salt was isolated, washed with diethyl ether and dried under vacuum.

Unless otherwise stated, each compound described in Table VI was obtained as a dihydrochloride salt.

Table VI



5

No. & Note	R ¹	R ²
[1]	2-[2-(<u>N,N</u> -dimethylcarbamoyl)pyrrolidin-1-yl]ethoxy	hydrogen
[2]	2-[2-(<u>N</u> -methylcarbamoyl)pyrrolidin-1-yl]ethoxy	hydrogen
[3]	2-(2-carbamoylpyrrolidin-1-yl)ethoxy	hydrogen
[4]	2-(2-piperidinocarbonylpyrrolidin-1-yl)ethoxy	hydrogen
[5]	2-(2-morpholinocarbonylpyrrolidin-1-yl)ethoxy	hydrogen
[6]	2-[2-(4-methylpiperazin-1-ylcarbonyl)pyrrolidin-1-yl]ethoxy	hydrogen
[7]	2-[2-(pyrrolidin-1-ylcarbonyl)pyrrolidin-1-yl]ethoxy	hydrogen
[8]	2-(2-methylpyrrolidin-1-yl)ethoxy	hydrogen
[9]	2-(2-methoxymethylpyrrolidin-1-yl)ethoxy	hydrogen
[10]	3-pyridylmethoxy	hydrogen
[11]	4-pyridylmethoxy	hydrogen

Notes

- [1] The free base was obtained from the chromatographic purification and gave the following data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 1.8-1.95 (m, 3H), 2.05-2.2 (m, 1H), 2.7 (s, 3H), 3.0 (s, 3H), 3.35 (m, 1H), 3.8-3.9 (m, 2H), 4.02 (s, 3H), 4.5 (m, 2H), 4.8 (m, 2H), 6.06 (s, 2H), 6.96 (s, 3H), 7.35 (s, 1H), 8.15 (s, 1H), 8.9 (s, 1H); Mass Spectrum: M+H⁺ 480.

The (2S)-1-(2-hydroxyethyl)-N,N-dimethylpyrrolidine-2-carboxamide used as a starting material was prepared as follows :-

- 15 A mixture of 1-(tert-butoxycarbonyl)-L-proline (10.75 g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (10.6 g), dimethylamine hydrochloride (5.33 g),

4-dimethylaminopyridine (6.1 g) and methylene chloride (200 ml) was stirred at ambient temperature for 4 hours. The mixture was poured into water. The organic layer was separated, washed in turn with a 1N aqueous potassium hydrogen sulphate solution, with a 5% aqueous sodium bicarbonate solution and brine, dried over magnesium sulphate and 5 evaporated to give 1-(*tert*-butoxycarbonyl)-N,N-dimethyl-L-prolinamide (11.2 g); NMR Spectrum: (CDCl₃) 1.4 and 1.5 (2 s, 9H), 1.8-1.9 (m, 2H), 1.95-2.2 (m, 2H), 3.0 and 3.1 (2 d, 6H), 3.35-3.6 (m, 2H), 4.55 and 4.7 (2 m, 1H).

A mixture of a portion (0.24 g) of the material so obtained and trifluoroacetic acid (3 ml) was stirred at ambient temperature for 2 hours. The mixture was evaporated and the 10 residue was triturated under diethyl ether. A slight excess of a 2M solution of hydrogen chloride in diethyl ether was added and the precipitate was isolated and dried under vacuum to give N,N-dimethyl-L-prolinamide hydrochloride salt (0.25 g); NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 1.7-2.0 (m, 3H), 2.3-2.5 (m, 1H), 2.95 (s, 3H), 3.05 (s, 3H), 3.1-3.4 (m, 2H), 4.6 (m, 1H).

15 A mixture of N,N-dimethyl-L-prolinamide hydrochloride salt (6.3 g), 2-bromoethanol (3.8 ml), potassium carbonate (14 g) and acetonitrile (70 ml) was stirred and heated to reflux for 16 hours. The mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography on silica using a 24:1 mixture of methylene chloride and a saturated methanolic ammonia solution as eluent. There was thus obtained
20 (2S)-1-(2-hydroxyethyl)-N,N-dimethylpyrrolidine-2-carboxamide (3.4 g); NMR Spectrum: (CDCl₃) 1.6 (m, 1H), 1.6-2.0 (m, 4H), 2.1-2.3 (m, 2H), 2.4 (m, 1H), 2.9 (m, 1H), 3.0 (s, 3H), 3.05 (s, 3H), 3.25-3.4 (m, 2H), 3.75 (m, 1H), 3.9 (m, 1H), 5.1 (br s, 1H); Mass Spectrum: M+H⁺ 187.

[2] (2S)-1-(2-Hydroxyethyl)-N-methylprolinamide was used as a starting material. The 25 dihydrochloride salt gave the following data; Mass Spectrum: M+H⁺ 466.

The (2S)-1-(2-hydroxyethyl)-N-methylprolinamide used as a starting material was obtained as follows :-

A mixture of 1-(*tert*-butoxycarbonyl)-L-proline (5.4 g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (5.3 g), methylamine hydrochloride (2.2 g), 4-dimethylaminopyridine 30 (3 g) and methylene chloride (50 ml) was stirred at ambient temperature for 16 hours. The resultant mixture was poured in water and the organic layer was separated, washed in turn with a 1M aqueous potassium hydrogen sulphate solution, a saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulphate and evaporated. There was

thus obtained 1-(*tert*-butoxycarbonyl)-N-methyl-L-prolinamide (5.6 g); Mass Spectrum: M+H⁺ 229.

A mixture of a portion (4.4 g) of the material so obtained and trifluoroacetic acid (10 ml) was stirred at ambient temperature for 2 hours. The mixture was evaporated and the residue was triturated under diethyl ether. The resultant solid was isolated, washed with diethyl ether and dried under vacuum. There was thus obtained to give N-methyl-L-prolinamide trifluoroacetic acid salt (3.7 g); NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 1.85-2.05 (m, 3H), 2.2-2.3 (m, 1H), 2.73 (s, 3H), 3.2-3.4 (m, 2H), 4.2 (m, 1H).

A mixture of a portion (2.5 g) of the material so obtained, 2-bromoethanol (2.15 ml), 10 potassium carbonate (5.5 g) and acetonitrile (20 ml) was stirred and heated to reflux for 18 hours. The mixture was cooled to ambient temperature, filtered and evaporated and the residue was purified by column chromatography on silica using a 49:1 mixture of methylene chloride and a saturated methanolic ammonia solution as eluent. There was thus obtained (2S)-1-(2-hydroxyethyl)-N-methylprolinamide (0.5 g); NMR Spectrum: (CDCl₃) 1.6-2.0 (m, 4H), 2.1-2.3 (m, 1H), 2.3-2.45 (m, 1H), 2.6-2.7 (m, 1H), 2.85 (d, 3H), 2.8-2.9 (m, 1H), 3.1-3.2 (m, 1H), 3.2-3.3 (m, 1H), 3.6-3.8 (m, 2H); Mass Spectrum: M+H⁺ 173.

[3] (2S)-1-(2-Hydroxyethyl)prolinamide was used as a starting material. The dihydrochloride salt gave the following data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 1.75-2.02(m, 2H), 2.03-2.19 (m, 1H), 2.56-2.67 (m, 1H), 3.3-3.43 (m, 1H), 3.7-3.91 (m, 3H), 4.03 (s, 3H), 4.28-4.43 (m, 1H), 4.45-4.65 (m, 2H), 6.08 (s, 2H), 6.94-7.04 (m, 3H), 7.42 (s, 1H), 8.21 (s, 1H), 8.88 (s, 1H); Mass Spectrum: M+H⁺ 452.

The (2S)-1-(2-hydroxyethyl)prolinamide used as a starting material was prepared by the reaction of L-prolinamide and 2-bromoethanol using an analogous procedure to that described in Note [2] immediately above. There was thus obtained the required starting material; NMR Spectrum: (CDCl₃) 1.6-2.0 (m, 4H), 2.1-2.25 (m, 1H), 2.35-2.45 (m, 1H), 2.6-2.7 (m, 1H), 2.8-3.0 (m, 1H), 3.1 (m, 1H), 3.2-3.3 (m, 1H), 3.6-3.8 (m, 2H), 5.6 (br s, 1H), 7.4 (br s, 1H); Mass Spectrum: M+H⁺ 159.

[4] (2S)-1-(2-Hydroxyethyl)-2-piperidinocarbonylpyrrolidine was used as a starting material. The dihydrochloride salt gave the following data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 1.28-1.75 (m, 7H), 1.76-1.99 (m, 2H), 2.02-2.25 (m, 1H), 3.02-3.19 (m, 1H), 3.22-3.5 (m, 3H), 3.53-3.65 (m, 1H), 3.68-3.9 (m, 3H), 4.04 (s, 3H), 4.44-4.63 (m, 2H), 4.74-4.89 (m, 1H), 6.36 (s, 2H), 6.91-7.07 (m, 3H), 7.45 (s, 1H), 8.25 (s, 1H), 8.89 (s, 1H); Mass Spectrum: M+H⁺ 520.

The (2S)-1-(2-hydroxyethyl)-2-piperidinocarbonylpyrrolidine used as a starting material was prepared as follows :-

- Using analogous procedures to those described in Note [2] immediately above, 1-(*tert*-butoxycarbonyl)-L-proline was reacted with piperidine to give
- 5 (2S)-1-(*tert*-butoxycarbonyl)-2-piperidinocarbonylpyrrolidine which was deprotected and reacted with 2-bromoethanol. There was thus obtained the required starting material; NMR Spectrum: (CDCl_3) 1.5-1.9 (m, 10H), 1.9-2.0 (m, 1H), 2.1-2.2 (m, 1H), 2.4-2.5 (m, 1H), 2.55-2.65 (m, 1H), 2.8-2.9 (m, 1H), 3.3-3.7 (m, 6H), 4.3 (br s, 1H); Mass Spectrum: $M+H^+$ 227.
- 10 [5] (2S)-1-(2-Hydroxyethyl)-2-morpholinocarbonylpyrrolidine was used as a starting material. The dihydrochloride salt gave the following data; NMR Spectrum: (DMSO_d_6 and $\text{CF}_3\text{CO}_2\text{D}$) 1.3-1.5 (m, 2H), 1.8-2.0 (m, 3H), 2.15 (m, 2H), 3.2 (m, 1H), 3.3-3.9 (m, 8H), 4.05 (s, 3H), 4.55 (m, 2H), 4.8 (m, 1H), 6.1 (s, 2H), 7.0 (m, 3H), 7.4 (s, 1H), 8.2 (s, 1H), 8.9 (s, 1H); Mass Spectrum: $M+H^+$ 522.
- 15 The (2S)-1-(2-hydroxyethyl)-2-morpholinocarbonylpyrrolidine used as a starting material was prepared as follows :-
- Using analogous procedures to those described in Note [2] immediately above, 1-(*tert*-butoxycarbonyl)-L-proline was reacted with morpholine to give
- (2S)-1-(*tert*-butoxycarbonyl)-2-morpholinocarbonylpyrrolidine which was deprotected and
- 20 reacted with 2-bromoethanol. There was thus obtained the required starting material; NMR Spectrum: (CDCl_3) 1.7-2.0 (m, 4H), 2.1-2.2 (m, 1H), 2.4-2.5 (m, 1H), 2.6-2.7 (m, 1H), 2.8-2.9 (m, 1H), 3.3-3.4 (m, 2H), 3.4-3.8 (m, 10H); Mass Spectrum: $M+H^+$ 229.
- [6] (2S)-1-(2-Hydroxyethyl)-2-(4-methylpiperazin-1-ylcarbonyl)pyrrolidine was used as a starting material. The free base was obtained from the chromatographic purification and gave
- 25 the following data; NMR Spectrum: (CDCl_3) 1.41-1.49 (m, 2H), 1.81-1.91 (m, 2H), 1.92-2.02 (m, 1H), 2.09-2.2 (m, 1H), 2.28 (s, 3H), 2.29-2.36 (m, 2H), 2.37-2.48 (m, 2H), 2.49-2.57 (m, 1H), 2.93-3.03 (m, 1H), 3.19-3.28 (m, 1H), 3.35-3.42 (m, 1H), 3.56-3.77 (m, 3H), 4.01 (s, 3H), 4.25-4.38 (m, 2H), 6.03 (s, 2H), 6.4-6.45 (m, 1H), 6.69 (d, 1H), 6.91 (m, 1H), 7.04 (s, 1H), 7.24 (s, 1H), 7.52 (d, 1H); Mass Spectrum: $M+H^+$ 535.
- 30 The (2S)-1-(2-hydroxyethyl)-2-(4-methylpiperazin-1-ylcarbonyl)pyrrolidine used as a starting material was prepared as follows :-

Using analogous procedures to those described in Note [2] immediately above, 1-(*tert*-butoxycarbonyl)-L-proline was reacted with 1-methylpiperazine to give

(2S)-1-(*tert*-butoxycarbonyl)-2-(4-methylpiperazin-1-ylcarbonyl)pyrrolidine which was deprotected and reacted with 2-bromoethanol. There was thus obtained the required starting material; NMR Spectrum: (CDCl_3) 1.7-2.05 (m, 4H), 2.1-2.25 (m, 1H), 2.32 (s, 3H), 2.35-2.5 (m, 4H), 2.6-2.7 (m, 1H), 2.8-2.9 (m, 1H), 3.3-3.7 (m, 8H), 4.15 (br s, 1H); Mass Spectrum:

5 $\text{M}+\text{H}^+$ 242.

[7] (2S)-1-(2-Hydroxyethyl)-2-(pyrrolidin-1-ylcarbonyl)pyrrolidine was used as a starting material. The dihydrochloride salt gave the following data; NMR Spectrum: (DMSO_d_6 and $\text{CF}_3\text{CO}_2\text{D}$) 1.29-1.52 (m, 2H), 1.55-2.03 (m, 5H), 2.07-2.23 (m, 1H), 2.93-3.08 (m, 1H), 3.18-3.45 (m, 3H), 3.46-3.59 (m, 1H), 3.72-3.93 (m, 3H), 4.03 (s, 3H), 4.43-4.71 (m, 3H), 6.09 (s, 10 2H), 7.94-7.06 (m, 3H), 7.39 (s, 1H), 8.2 (s, 1H), 8.89 (s, 1H); Mass Spectrum: $\text{M}-\text{H}^-$ 504.

The (2S)-1-(2-hydroxyethyl)-2-(pyrrolidin-1-ylcarbonyl)pyrrolidine used as a starting material was prepared as follows :-

Using analogous procedures to those described in Note [2] immediately above,

1-(*tert*-butoxycarbonyl)-L-proline was reacted with pyrrolidine to give

15 (2S)-1-(*tert*-butoxycarbonyl)-2-(pyrrolidin-1-ylcarbonyl)pyrrolidine which was deprotected and reacted with 2-bromoethanol. There was thus obtained the required starting material; NMR Spectrum: (CDCl_3) 1.7-2.05 (m, 8H), 2.1-2.3 (m, 1H), 2.4-2.5 (m, 1H), 2.55-2.7 (m, 1H), 2.8-2.9 (m, 1H), 3.2-3.3 (m, 2H), 3.4-3.7 (m, 5H), 4.1 (br s, 1H); Mass Spectrum: $\text{M}+\text{H}^+$ 213.

20 [8] (2R)-1-(2-Hydroxyethyl)-2-methylpyrrolidine was used as a starting material. The dihydrochloride salt gave the following data; NMR Spectrum: (DMSO_d_6 and $\text{CF}_3\text{CO}_2\text{D}$) 1.45 (d, 3H), 1.6-1.7 (m, 1H), 1.9-2.1 (m, 2H), 2.1-2.3 (m, 1H), 3.35 (m, 1H), 3.5-3.7 (m, 2H), 3.7-3.8 (m, 1H), 3.9 (m, 1H), 4.05 (s, 3H), 4.6 (br s, 2H), 6.1 (s, 2H), 7.0 (s, 3H), 7.45 (s, 1H), 8.25 (s, 1H), 8.9 (s, 1H); Mass Spectrum: $\text{M}+\text{H}^+$ 423.

25 The (2R)-1-(2-hydroxyethyl)-2-methylpyrrolidine used as a starting material was obtained as follows :-

A mixture of (2R)-2-methylpyrrolidine (0.853 g), 2-bromoethanol (1.1 ml), potassium carbonate (2.8 g) and acetonitrile (10 ml) was stirred and heated to reflux for 18 hours. The mixture was filtered and the filtrate was evaporated. The resultant residue was purified by 30 column chromatography on silica using a 49:1 mixture of methylene chloride and a saturated methanolic ammonia solution as eluent. There was thus obtained (2R)-1-(2-hydroxyethyl)-2-methylpyrrolidine (0.35 g); NMR Spectrum : (CDCl_3) 1.1 (d, 3H), 1.3-1.5 (m, 1H), 1.6-1.8

(m, 3H), 1.95 (m, 1H), 2.15 (m, 1H), 2.28 (m, 1H), 2.4-2.5 (m, 1H), 2.95-3.05 (m, 1H), 3.2 (m, 1H), 3.5-3.8 (m, 2H); Mass Spectrum: M+H⁺ 130.

[9] (2S)-1-(2-Hydroxyethyl)-2-methoxymethylpyrrolidine was used as a starting material. The dihydrochloride salt gave the following data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 5 1.4-1.5 (m, 1H), 1.65-1.8 (m, 1H), 1.8-2.0 (m, 1H), 2.0-2.12 (m, 1H), 2.12-2.25 (m, 1H), 3.35 (s, 3H), 3.7 (m, 4H), 3.8-4.0 (m, 2H), 4.05 (s, 3H), 4.6 (m, 2H), 6.1 (s, 2H), 7.0 (m, 3H), 7.45 (s, 1H), 8.25 (s, 1H), 8.9 (s, 1H); Mass Spectrum: M+H⁺ 453.

The (2S)-1-(2-hydroxyethyl)-2-methoxymethylpyrrolidine used as a starting material was obtained as follows :-

10 Using an analogous procedure to those described in Note [8] immediately above, (2S)-2-methoxymethylpyrrolidine was reacted with 2-bromoethanol to give (2S)-1-(2-hydroxyethyl)-2-methoxymethylpyrrolidine; NMR Spectrum: (CDCl₃) 1.5-1.65 (m, 1H), 1.65-1.8 (m, 2H), 1.8-2.0 (m, 2H), 2.3 (m, 1H), 2.6 (m, 1H), 2.8 (m, 1H), 2.95-3.05 (m, 1H), 3.17 (m, 1H), 3.3 (t, 1H), 3.35 (t, 1H), 3.37 (s, 3H), 3.5-3.7 (m, 2H).

15 [10] The dihydrochloride salt gave the following data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 4.05 (s, 3H), 5.6 (s, 2H), 6.1 (s, 2H), 7.0 (s, 3H), 7.6 (s, 1H), 8.2 (m, 1H), 8.3 (s, 1H), 8.8 (d, 1H), 8.9 (s, 1H), 9.05 (d, 1H), 9.2 (s, 1H); Mass Spectrum: M+H⁺ 403.

[11] The dihydrochloride salt gave the following data; NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 4.1 (s, 3H), 5.75 (s, 2H), 6.1 (s, 2H), 7.0 (s, 3H), 7.5 (s, 1H), 8.2 (d, 2H), 8.3 (s, 1H), 8.9 (s, 1H), 9.05 (d, 2H); Mass Spectrum: M+H⁺ 403.

20

Example 28

Pharmaceutical compositions

The following illustrate representative pharmaceutical dosage forms of the invention 25 as defined herein (the active ingredient being termed "Compound X"), for therapeutic or prophylactic use in humans:

(a)	Tablet I	mg/tablet
	Compound X.....	100
30	Lactose Ph.Eur.....	182.75
	Croscarmellose sodium.....	12.0
	Maize starch paste (5% w/v paste).....	2.25
	Magnesium stearate.....	3.0

(b)	Tablet II	mg/tablet
	Compound X.....	50
	Lactose Ph.Eur.....	223.75
	Croscarmellose sodium.....	6.0
5	Maize starch.....	15.0
	Polyvinylpyrrolidone (5% w/v paste).....	2.25
	Magnesium stearate.....	3.0
(c)	Tablet III	mg/tablet
10	Compound X.....	1.0
	Lactose Ph.Eur.....	93.25
	Croscarmellose sodium.....	4.0
	Maize starch paste (5% w/v paste).....	0.75
	Magnesium stearate.....	1.0
15		
(d)	Capsule	mg/capsule
	Compound X.....	10
	Lactose Ph.Eur.....	488.5
	Magnesium.....	1.5
20		
(e)	Injection I	(50 mg/ml)
	Compound X.....	5.0% w/v
	1M Sodium hydroxide solution.....	15.0% v/v
	0.1M Hydrochloric acid (to adjust pH to 7.6)	
25	Polyethylene glycol 400.....	4.5% w/v
	Water for injection to 100%	
(f)	Injection II	(10 mg/ml)
	Compound X.....	1.0% w/v
30	Sodium phosphate BP.....	3.6% w/v
	0.1M Sodium hydroxide solution.....	15.0% v/v
	Water for injection to 100%	

(g)	Injection III	(1mg/ml, buffered to pH6)
	Compound X.....	0.1% w/v
	Sodium phosphate BP.....	2.26% w/v
	Citric acid.....	0.38% w/v
5	Polyethylene glycol 400.....	3.5% w/v
	Water for injection to 100%	

(h)	Aerosol I	mg/ml
	Compound X.....	10.0
10	Sorbitan trioleate.....	13.5
	Trichlorofluoromethane.....	910.0
	Dichlorodifluoromethane.....	490.0

(i)	Aerosol II	mg/ml
15	Compound X.....	0.2
	Sorbitan trioleate.....	0.27
	Trichlorofluoromethane.....	70.0
	Dichlorodifluoromethane.....	280.0
	Dichlorotetrafluoroethane.....	1094.0

(j)	Aerosol III	mg/ml
	Compound X.....	2.5
	Sorbitan trioleate.....	3.38
	Trichlorofluoromethane.....	67.5
25	Dichlorodifluoromethane.....	1086.0
	Dichlorotetrafluoroethane.....	191.6

(k)	Aerosol IV	mg/ml
	Compound X.....	2.5
30	Soya lecithin.....	2.7
	Trichlorofluoromethane.....	67.5
	Dichlorodifluoromethane.....	1086.0
	Dichlorotetrafluoroethane.....	191.6

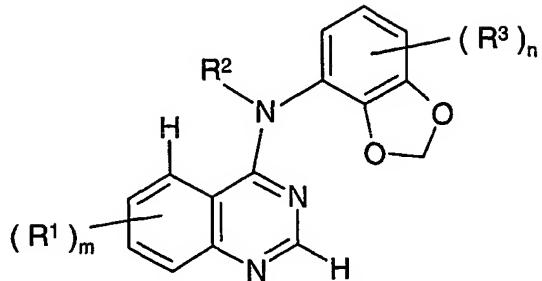
(l)	Ointment	ml
	Compound X.....	40 mg
	Ethanol.....	300 µl
5	Water.....	300 µl
	1-Dodecylazacycloheptan-2-one.....	50 µl
	Propylene glycol.....	to 1 ml

Note

- 10 The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate. The aerosol formulations (h)-(k) may be used in conjunction with standard, metered dose aerosol dispensers, and the suspending agents sorbitan trioleate and soya lecithin may be replaced by an alternative
15 suspending agent such as sorbitan monooleate, sorbitan sesquioleate, polysorbate 80, polyglycerol oleate or oleic acid.

CLAIMS

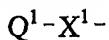
1. A quinazoline derivative of the Formula I



I

5 wherein m is 0, 1, 2 or 3;

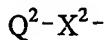
each R¹ group, which may be the same or different, is selected from halogeno, trifluoromethyl, cyano, isocyano, nitro, hydroxy, mercapto, amino, formyl, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphanyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, (3-6C)alkenoylamino, N-(1-6C)alkyl-(3-6C)alkenoylamino, (3-6C)alkynoylamino, N-(1-6C)alkyl-(3-6C)alkynoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and 15 N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



wherein X¹ is a direct bond or is selected from O, S, SO, SO₂, N(R⁴), CO, CH(OR⁴), CON(R⁴), N(R⁴)CO, SO₂N(R⁴), N(R⁴)SO₂, OC(R⁴)₂, SC(R⁴)₂ and N(R⁴)C(R⁴)₂, wherein R⁴ is hydrogen or (1-6C)alkyl, and Q¹ is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-20 (1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl, or (R¹)_m is (1-3C)alkylenedioxy,

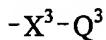
and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO₂, N(R⁵), CO, CH(OR⁵), CON(R⁵), N(R⁵)CO, SO₂N(R⁵), N(R⁵)SO₂, CH=CH and C≡C wherein 25 R⁵ is hydrogen or (1-6C)alkyl or, when the inserted group is N(R⁵), R⁵ may also be (2-6C)alkanoyl,

and wherein any $\text{CH}_2=\text{CH}-$ or $\text{HC}\equiv\text{C}-$ group within a R^1 substituent optionally bears at the terminal $\text{CH}_2=$ or $\text{HC}\equiv$ position a substituent selected from halogeno, carboxy, carbamoyl, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl or 5 from a group of the formula :



wherein X^2 is a direct bond or is selected from CO and $\text{N}(\text{R}^6)\text{CO}$, wherein R^6 is hydrogen or (1-6C)alkyl, and Q^2 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

10 and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphanyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, 15 (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



20 wherein X^3 is a direct bond or is selected from O , S , SO , SO_2 , $\text{N}(\text{R}^7)$, CO , $\text{CH}(\text{OR}^7)$, $\text{CON}(\text{R}^7)$, $\text{N}(\text{R}^7)\text{CO}$, $\text{SO}_2\text{N}(\text{R}^7)$, $\text{N}(\text{R}^7)\text{SO}_2$, $\text{C}(\text{R}^7)_2\text{O}$, $\text{C}(\text{R}^7)_2\text{S}$ and $\text{N}(\text{R}^7)\text{C}(\text{R}^7)_2$, wherein R^7 is hydrogen or (1-6C)alkyl, and Q^3 is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

25 and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R^1 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphanyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, 30 di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl,

N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :

$-X^4-R^8$

wherein X^4 is a direct bond or is selected from O and $N(R^9)$, wherein R^9 is hydrogen or
 5 (1-6C)alkyl, and R^8 is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl,
 cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl,
 (2-6C)alkanoylamino-(1-6C)alkyl or (1-6C)alkoxycarbonylamino-(1-6C)alkyl,
 or from a group of the formula :

$-X^5-Q^4$

10 wherein X^5 is a direct bond or is selected from O, $N(R^{10})$ and CO, wherein R^{10} is hydrogen or
 (1-6C)alkyl, and Q^4 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl
 or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same
 or different, selected from halogeno, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl and
 (1-6C)alkoxy,

15 and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2
 oxo or thioxo substituents;

R^2 is hydrogen or (1-6C)alkyl;

n is 0, 1, 2 or 3; and

R^3 is halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl,

20 (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy,
 (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl,
 (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl,
N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino,
N-(1-6C)alkyl-(2-6C)alkanoylamino, (3-6C)alkenoylamino, N-(1-6C)alkyl-
 25 (3-6C)alkenoylamino, (3-6C)alkynoylamino, N-(1-6C)alkyl-(3-6C)alkynoylamino,
N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and
N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :

$-X^6-R^{11}$

wherein X^6 is a direct bond or is selected from O and $N(R^{12})$, wherein R^{12} is hydrogen or
 30 (1-6C)alkyl, and R^{11} is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl,
 cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl or
 di-[(1-6C)alkyl]amino-(1-6C)alkyl, or from a group of the formula :

$-X^7-Q^5$

wherein X^7 is a direct bond or is selected from O, S, SO, SO₂, N(R¹³), CO, CH(OR¹³), CON(R¹³), N(R¹³)CO, SO₂N(R¹³), N(R¹³)SO₂, C(R¹³)₂O, C(R¹³)₂S and N(R¹³)C(R¹³)₂, wherein R¹³ is hydrogen or (1-6C)alkyl, and Q⁵ is aryl, aryl-(1-6C)alkyl, heteroaryl,

5 heteroaryl-(1-6C)alkyl, heterocycll or heterocycll-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl and (1-6C)alkoxy, and any heterocycll group within Q⁵ optionally bears 1 or 2 oxo or thioxo substituents, or a pharmaceutically-acceptable salt thereof.

10

2. A quinazoline derivative of the Formula I according to claim 1, or a pharmaceutically-acceptable salt thereof, wherein each of R², n and R³ has any of the meanings defined in claim 1,

m is 1 or 2, and each R¹ group, which may be the same or different, is selected from 15 halogeno, trifluoromethyl, hydroxy, amino, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, (3-6C)alkenoylamino, N-(1-6C)alkyl-(3-6C)alkenoylamino, 20 or from a group of the formula :

Q^1-X^1-

wherein X¹ is a direct bond or is selected from O, N(R⁴), CON(R⁴), N(R⁴)CO and OC(R⁴)₂

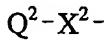
wherein R⁴ is hydrogen or (1-6C)alkyl, and Q¹ is aryl, aryl-(1-6C)alkyl, cycloalkyl-

(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocycll or heterocycll-(1-6C)alkyl,

25 and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent are optionally separated by the insertion into the chain of a group selected from O, N(R⁵), CON(R⁵), N(R⁵)CO, CH=CH and C≡C wherein R⁵ is hydrogen or (1-6C)alkyl, or, when the inserted group is N(R⁵), R⁵ may also be (2-6C)alkanoyl,

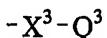
and wherein any CH₂=CH- or HC≡C- group within a R¹ substituent optionally bears at 30 the terminal CH₂= or HC≡ position a substituent selected from carbamoyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, amino-(1-6C)alkyl,

(1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl or from a group of the formula :



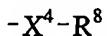
wherein X^2 is a direct bond or is CO or $N(R^6)CO$, wherein R^6 is hydrogen or (1-6C)alkyl, and
5 Q^2 is heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group a substituent selected from hydroxy, amino, (1-6C)alkoxy, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (2-6C)alkanoyloxy, (2-6C)alkanoylamino and N-(1-6C)alkyl-(2-6C)alkanoylamino, or from a group of the
10 formula :

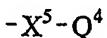


wherein X^3 is a direct bond or is selected from O, $N(R^6)$, $CON(R^7)$, $N(R^7)CO$ and $C(R^7)_2O$, wherein R^7 is hydrogen or (1-6C)alkyl, and Q^3 is heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

15 and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R^1 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, hydroxy, amino, carbamoyl, (1-6C)alkyl, (1-6C)alkoxy, N-(1-6C)alkylcarbamoyl and N,N-di-[(1-6C)alkyl]carbamoyl, or optionally bears 1 substituent selected from a group of the formula :



20 wherein X^4 is a direct bond or is selected from O and $N(R^9)$, wherein R^9 is hydrogen or (1-6C)alkyl, and R^8 is hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl or (1-6C)alkoxycarbonylamino-(1-6C)alkyl, and from a
25 group of the formula :



wherein X^5 is a direct bond or is selected from O, $N(R^{10})$ and CO, wherein R^{10} is hydrogen or (1-6C)alkyl, and Q^4 is heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl and
30 (1-6C)alkoxy,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo substituents.

3. A quinazoline derivative of the Formula I according to claim 1, or a pharmaceutically-acceptable salt thereof, wherein each of R², n and R³ has any of the meanings defined in claim 1,

m is 2 and each R¹ group, which may be the same or different, is located at the
5 6- and/or 7-positions and is selected from hydroxy, amino, methyl, ethyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, methylamino, ethylamino, dimethylamino, diethylamino, acetamido, propionamido, benzyloxy, 2-pyrrol-1-yethoxy, 3-pyrrol-1-ylpropoxy, 2-imidazol-1-yethoxy, 3-imidazol-1-ylpropoxy, 2-(1,2,3-triazol-1-yl)ethoxy, 3-(1,2,3-triazol-1-yl)propoxy, 2-(1,2,4-triazol-1-yl)ethoxy, 3-(1,2,4-triazol-1-yl)propoxy,
10 2-pyridylmethoxy, 3-pyridylmethoxy, 4-pyridylmethoxy, 2-tetrahydropyran-4-yethoxy, 3-tetrahydropyran-4-ylpropoxy, 2-pyrrolidin-1-yethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-yethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, piperidin-4-ylmethoxy, 2-piperidin-3-yethoxy, 3-piperidin-3-ylpropoxy, 2-piperidin-4-yethoxy, 3-piperidin-4-ylpropoxy, 2-homopiperidin-1-yethoxy, 3-homopiperidin-1-ylpropoxy, 2-piperazin-1-yethoxy, 3-piperazin-1-ylpropoxy, 4-piperazin-1-ylbutoxy,
15 20 2-homopiperazin-1-yethoxy or 3-homopiperazin-1-ylpropoxy,
and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent are optionally separated by the insertion into the chain of a group selected from O, NH, CH=CH and C≡C,
and wherein any CH₂ or CH₃ group within a R¹ substituent optionally bears on each
25 said CH₂ or CH₃ group a substituent selected from hydroxy, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diethylamino, diisopropylamino, N-ethyl-N-methylamino, N-isopropyl-N-methylamino, N-isobutyl-N-methylamino, N-allyl-N-methylamino, acetoxy, acetamido, N-methylacetamido, 2-pyridyloxy, 3-pyridyloxy and 4-pyridyloxy,
30 and wherein any phenyl, pyrrolyl, imidazolyl, triazolyl, pyridyl or heterocyclyl group within a substituent on R¹ optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, cyano, hydroxy, amino, carbamoyl,

methyl, ethyl, N-methylcarbamoyl, N,N-dimethylcarbamoyl, methoxy, methoxymethyl and morpholinomethyl, and a pyrrolidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl or homopiperazin-1-yl group within a R¹ substituent is optionally N-substituted with methyl, ethyl, 2-methoxyethyl, 3-methoxypropyl, cyanomethyl, 2-aminoethyl, 3-aminopropyl,
5 2-methylaminoethyl, 3-methylaminopropyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, 2-pyrrolidin-1-yethyl, 3-pyrrolidin-1-ylpropyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-piperazin-1-yethyl or 3-piperazin-1-ylpropyl, the last 8 of which substituents each optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, methyl and methoxy,
10 and wherein any heterocyclyl group within a substituent on R¹ optionally bears 1 or 2 oxo substituents.

4. A quinazoline derivative of the Formula I according to claim 1, or a pharmaceutically-acceptable salt thereof, wherein each of m, R¹, n and R³ has any of the
15 meanings defined in claim 1, and R² is hydrogen.

5. A quinazoline derivative of the Formula I according to claim 1, or a pharmaceutically-acceptable salt thereof, wherein each of m, R¹ and R² has any of the meanings defined in claim 1,
20 n is 1 or 2 and the R³ groups, which may be the same or different, are located at the 5- and/or 6-positions of the 2,3-methylenedioxyphenyl group and are selected from halogeno, trifluoromethyl, cyano, hydroxy, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl and (1-6C)alkoxy.

6. A quinazoline derivative of the Formula I according to claim 1, or a pharmaceutically-acceptable salt thereof, wherein each of m, R¹ and R² has any of the
25 meanings defined in claim 1 and n is 0.

7. A quinazoline derivative of the Formula I according to claim 1 wherein :
m is 1 or 2 and each R¹ group, which may be the same or different, is located at the
30 6- and/or 7-positions and is selected from hydroxy, amino, methyl, ethyl, propyl, butyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, methylamino, ethylamino, dimethylamino, diethylamino, acetamido, propionamido, 2-imidazol-1-yethoxy, 2-(1,2,4-triazol-1-yl)ethoxy, 2-pyrrolidin-1-yethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy,

pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy,
3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy,
2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-
4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy,
5 piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, piperidin-4-ylmethoxy,
2-piperidin-3-ylethoxy, 3-piperidin-3-ylpropoxy, 2-piperidin-4-ylethoxy,
3-piperidin-4-ylpropoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy,
2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 4-piperazin-1-ylbutoxy,
2-homopiperazin-1-ylethoxy and 3-homopiperazin-1-ylpropoxy,

10 and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent
are optionally separated by the insertion into the chain of a group selected from O, NH,
CH=CH and C≡C,

and wherein any CH₂ or CH₃ group within a R¹ substituent optionally bears on each
said CH₂ or CH₃ group a substituent selected from hydroxy, amino, methoxy,
15 methylsulphonyl, methylamino, dimethylamino, diethylamino, N-ethyl-N-methylamino,
N-isopropyl-N-methylamino, N-methyl-N-propylamino and acetoxy;

and wherein any heteroaryl or heterocyclyl group within a substituent on R¹ optionally
bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro,
trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl, methoxy, N-methylcarbamoyl and
20 N,N-dimethylcarbamoyl and a pyrrolidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl or
homopiperazin-1-yl group within a R¹ substituent is optionally N-substituted with
2-methoxyethyl, 3-methoxypropyl, cyanomethyl, 2-aminoethyl,
3-aminopropyl, 2-methylaminoethyl, 3-methylaminopropyl, 2-dimethylaminoethyl,
3-dimethylaminopropyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, 2-morpholinoethyl,
25 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-piperazin-1-ylethyl or
3-piperazin-1-ylpropyl, the last 8 of which substituents each optionally bears 1 or 2
substituents, which may be the same or different, selected from fluoro, chloro, methyl and
methoxy,

and wherein any heterocyclyl group within a substituent on R¹ optionally bears 1 or 2
30 oxo substituents;

R² is hydrogen;

n is 0 or 1 and the R³ group, if present, is located at the 5- or 6-position of the 2,3-methylenedioxyphenyl group and is selected from fluoro, chloro, trifluoromethyl, cyano, hydroxy, methyl, ethyl, vinyl, allyl, ethynyl, methoxy and ethoxy; or a pharmaceutically-acceptable acid-addition salt thereof.

5

8. A quinazoline derivative of the Formula I according to claim 1 wherein :

m is 2 and each R¹ group, which may be the same or different, is located at the 6- and/or 7-positions and is selected from hydroxy, amino, methyl, ethyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, methylamino, ethylamino, dimethylamino, diethylamino, 10 acetamido, propionamido, benzyloxy, 2-pyrrol-1-ylethoxy, 3-pyrrol-1-ylpropoxy, 2-imidazol-1-ylethoxy, 3-imidazol-1-ylpropoxy, 2-(1,2,3-triazol-1-yl)ethoxy, 3-(1,2,3-triazol-1-yl)propoxy, 2-(1,2,4-triazol-1-yl)ethoxy, 3-(1,2,4-triazol-1-yl)propoxy, 2-pyridylmethoxy, 3-pyridylmethoxy, 4-pyridylmethoxy, 2-tetrahydropyran-4-ylethoxy, 3-tetrahydropyran-4-ylpropoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 15 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, piperidin-4-ylmethoxy, 20 2-piperidin-3-ylethoxy, 3-piperidin-3-ylpropoxy, 2-piperidin-4-ylethoxy, 3-piperidin-4-ylpropoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 4-piperazin-1-ylbutoxy, 2-homopiperazin-1-ylethoxy or 3-homopiperazin-1-ylpropoxy,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent 25 are optionally separated by the insertion into the chain of a group selected from O, NH, CH=CH and C≡C,

and wherein any CH₂ or CH₃ group within a R¹ substituent optionally bears on each said CH₂ or CH₃ group a substituent selected from hydroxy, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diethylamino, diisopropylamino, 30 N-ethyl-N-methylamino, N-isopropyl-N-methylamino, N-isobutyl-N-methylamino, N-allyl-N-methylamino, acetoxy, acetamido, N-methylacetamido, 2-pyridyloxy, 3-pyridyloxy and 4-pyridyloxy,

and wherein any phenyl, pyrrolyl, imidazolyl, triazolyl, pyridyl or heterocyclyl group within a substituent on R¹ optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, cyano, hydroxy, amino, carbamoyl, methyl, ethyl, N-methylcarbamoyl, N,N-dimethylcarbamoyl, methoxy, methoxymethyl and 5 morpholinomethyl, and a pyrrolidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl or homopiperazin-1-yl group within a R¹ substituent is optionally N-substituted with methyl, ethyl, 2-methoxyethyl, 3-methoxypropyl, cyanomethyl, 2-aminoethyl, 3-aminopropyl, 2-methylaminoethyl, 3-methylaminopropyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, 2-morpholinoethyl, 3-morpholinopropyl, 10 2-piperidinoethyl, 3-piperidinopropyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl, the last 8 of which substituents each optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, methyl and methoxy,

and wherein any heterocyclyl group within a substituent on R¹ optionally bears 1 or 2 oxo substituents;

15 R² is hydrogen;

n is 0 or 1 and the R³ group, if present, is located at the 6-position of the 2,3-methylenedioxyphenyl group and is selected from chloro, bromo and trifluoromethyl; or a pharmaceutically-acceptable acid-addition salt thereof.

20 9. A quinazoline derivative of the Formula I according to claim 1 wherein :

m is 2 and the first R¹ group is located at the 6-position and is selected from hydroxy, methoxy, ethoxy and propoxy, and the second R¹ group is located at the 7-position and is selected from 2-dimethylaminoethoxy, 3-dimethylaminopropoxy, 4-dimethylaminobutoxy, 2-diethylaminoethoxy, 3-diethylaminopropoxy, 4-diethylaminobutoxy, 25 2-diisopropylaminoethoxy, 3-diisopropylaminopropoxy, 4-diisopropylaminobutoxy, 2-(N-isopropyl-N-methylamino)ethoxy, 3-(N-isopropyl-N-methylamino)propoxy, 4-(N-isopropyl-N-methylamino)butoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy, N-methylpyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 30 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, piperidin-3-yloxy, N-methylpiperidin-3-yloxy, piperidin-4-yloxy, N-methylpiperidin-4-yloxy,

piperidin-3-ylmethoxy, N-methylpiperidin-3-ylmethoxy, piperidin-4-ylmethoxy,
N-methylpiperidin-4-ylmethoxy, 2-piperidin-3-yloethoxy, 2-(N-methylpiperidin-3-yl)ethoxy,
3-piperidin-3-ylpropoxy, 3-(N-methylpiperidin-3-yl)propoxy, 2-piperidin-4-yloethoxy,
2-(N-methylpiperidin-4-yl)ethoxy, 3-piperidin-4-ylpropoxy,
5 3-(N-methylpiperidin-4-yl)propoxy, 2-(4-methylpiperazin-1-yl)ethoxy,
3-(4-methylpiperazin-1-yl)propoxy, 4-(4-methylpiperazin-1-yl)butoxy,
2-(4-cyanomethylpiperazin-1-yl)ethoxy, 3-(4-cyanomethylpiperazin-1-yl)propoxy,
4-(4-cyanomethylpiperazin-1-yl)butoxy, 2-[2-(4-methylpiperazin-1-yl)ethoxy]ethoxy,
2-methylsulphonyloethoxy and 3-methylsulphonylpropoxy,

10 and wherein any CH₂ group within the second R¹ group that is attached to two carbon atoms optionally bears a hydroxy group or acetoxy group on said CH₂ group,
and wherein any heterocyclyl group within the second R¹ group optionally bears 1 or 2 oxo substituents;

R² is hydrogen; and

15 n is 0 or n is 1 and the R³ group is located at the 5- or 6-position of the
2,3-methylenedioxyphenyl group and is selected from fluoro, chloro, trifluoromethyl, cyano,
methyl, ethyl, ethynyl, methoxy and ethoxy;
or a pharmaceutically-acceptable acid-addition salt thereof.

20 10. A quinazoline derivative of the Formula I according to claim 1 wherein :

m is 2 and the first R¹ group is a 6-methoxy group and the second R¹ group is located at the 7-position and is selected from 2-dimethylaminoethoxy, 3-dimethylaminopropoxy,
4-dimethylaminobutoxy, 2-diethylaminoethoxy, 3-diethylaminopropoxy,
4-diethylaminobutoxy, 2-diisopropylaminoethoxy, 3-diisopropylaminopropoxy,
25 4-diisopropylaminobutoxy, 2-(N-isopropyl-N-methylamino)ethoxy,
3-(N-isopropyl-N-methylamino)propoxy, 4-(N-isopropyl-N-methylamino)butoxy,
2-(N-isobutyl-N-methylamino)ethoxy, 3-(N-isobutyl-N-methylamino)propoxy,
4-(N-isobutyl-N-methylamino)butoxy, 2-(N-allyl-N-methylamino)ethoxy,
3-(N-allyl-N-methylamino)propoxy, 4-(N-allyl-N-methylamino)butoxy,
30 2-pyrrolidin-1-yloethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy,
pyrrolidin-3-yloxy, N-methylpyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy,
2-pyrrolidin-2-yloethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy,
3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-

- 4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy,
3-piperidinopropoxy, 4-piperidinobutoxy, piperidin-3-yloxy, N-methylpiperidin-3-yloxy,
piperidin-4-yloxy, N-methylpiperidin-4-yloxy, piperidin-3-ylmethoxy,
N-methylpiperidin-3-ylmethoxy, N-cyanomethylpiperidin-3-ylmethoxy,
- 5 piperidin-4-ylmethoxy, N-methylpiperidin-4-ylmethoxy, N-cyanomethylpiperidin-
4-ylmethoxy, 2-piperidin-3-ylethoxy, 2-(N-methylpiperidin-3-yl)ethoxy,
3-piperidin-3-ylpropoxy, 3-(N-methylpiperidin-3-yl)propoxy, 2-piperidin-4-ylethoxy,
2-(N-methylpiperidin-4-yl)ethoxy, 3-piperidin-4-ylpropoxy, 3-(N-methylpiperidin-
4-yl)propoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy,
- 10 4-homopiperidin-1-ylbutoxy, 2-piperazin-1-ylethoxy, 2-(4-methylpiperazin-1-yl)ethoxy,
3-piperazin-1-ylpropoxy, 3-(4-methylpiperazin-1-yl)propoxy, 4-piperazin-1-ylbutoxy,
4-(4-methylpiperazin-1-yl)butoxy, 2-(4-cyanomethylpiperazin-1-yl)ethoxy,
3-(4-cyanomethylpiperazin-1-yl)propoxy, 4-(4-cyanomethylpiperazin-1-yl)butoxy,
2-(2-piperazin-1-ylethoxy)ethoxy, 2-[2-(4-methylpiperazin-1-yl)ethoxy]ethoxy,
- 15 2-methylsulphonylethoxy, 3-methylsulphonylpropoxy, 2-tetrahydropyran-4-ylethoxy,
3-tetrahydropyran-4-ylpropoxy, 2-pyrrol-1-ylethoxy, 3-pyrrol-1-ylpropoxy,
2-(2-pyridyloxy)ethoxy, 3-(2-pyridyloxy)propoxy, 2-(3-pyridyloxy)ethoxy,
3-(3-pyridyloxy)propoxy, 2-(4-pyridyloxy)ethoxy, 3-(4-pyridyloxy)propoxy,
2-pyridylmethoxy, 3-pyridylmethoxy and 4-pyridylmethoxy,
- 20 and wherein any CH₂ group within the second R¹ group that is attached to two carbon
atoms optionally bears a hydroxy group on said CH₂ group,
and wherein any heteroaryl group within the second R¹ group optionally bears 1 or 2
substituents selected from chloro, cyano, hydroxy and methyl, and any heterocyclyl group
within the second R¹ group optionally bears 1 or 2 substituents selected from hydroxy, methyl
25 and oxo;
- R² is hydrogen; and
n is 0 or n is 1 and the R³ group is located at the 6-position of the
2,3-methylenedioxyphenyl group and is selected from chloro and bromo;
or a pharmaceutically-acceptable acid-addition salt thereof.
- 30
11. A quinazoline derivative of the Formula I according to claim 1 wherein :
m is 2 and the first R¹ group is a 6-methoxy group and the second R¹ group is located
at the 7-position and is selected from 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy,

2-morpholinoethoxy, 3-morpholinopropoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, piperidin-3-ylmethoxy, N-methylpiperidin-3-ylmethoxy, piperidin-4-ylmethoxy, N-methylpiperidin-4-ylmethoxy, 2-piperidin-3-ylethoxy,

5 2-(N-methylpiperidin-3-yl)ethoxy, 3-piperidin-3-ylpropoxy, 3-(N-methylpiperidin-3-yl)propoxy, 2-piperidin-4-ylethoxy, 2-(N-methylpiperidin-4-yl)ethoxy, 3-piperidin-4-ylpropoxy, 3-(N-methylpiperidin-4-yl)propoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 2-(4-cyanomethylpiperazin-1-yl)ethoxy, 3-(4-cyanomethylpiperazin-1-yl)propoxy,

10 2-[2-(4-methylpiperazin-1-yl)ethoxy]ethoxy, 2-methylsulphonylethoxy, 3-methylsulphonylpropoxy, 2-(4-pyridyloxy)ethoxy, 3-pyridylmethoxy and 2-cyanopyrid-4-ylmethoxy;

R² is hydrogen; and

n is 0 or n is 1 and the R³ group is located at the 6-position of the

15 2,3-methylenedioxyphenyl group and is selected from chloro and bromo; or a pharmaceutically-acceptable acid-addition salt thereof.

12. A quinazoline derivative of the Formula I according to claim 1 wherein :

m is 2 and the first R¹ group is a 6-methoxy group and the second R¹ group is located
20 at the 7-position and is selected from 3-(N-isopropyl-N-methylamino)propoxy, 3-pyrrolidin-1-ylpropoxy, 3-morpholinopropoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 3-piperidinopropoxy, N-methylpiperidin-4-ylmethoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 3-(4-cyanomethylpiperazin-1-yl)propoxy and 2-[2-(4-methylpiperazin-1-yl)ethoxy]ethoxy,
25 and wherein any CH₂ group within the second R¹ group that is attached to two carbon atoms optionally bears a hydroxy group on said CH₂ group;

R² is hydrogen; and

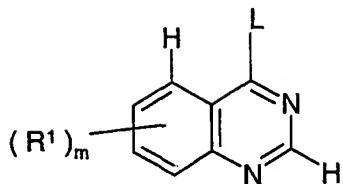
n is 0;

or a pharmaceutically-acceptable acid-addition salt thereof.

30

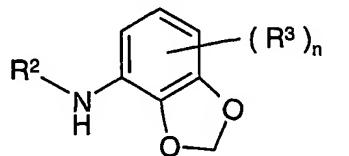
13. A quinazoline derivative of the Formula I according to claim 1 selected from : 6-methoxy-4-(2,3-methylenedioxyanilino)-7-(3-morpholinopropoxy)quinazoline,

- 6-methoxy-4-(2,3-methylenedioxyanilino)-7-[3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy]quinazoline,
- 6-methoxy-4-(2,3-methylenedioxyanilino)-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,
- 6-methoxy-4-(2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]quinazoline,
- 5 6-methoxy-4-(2,3-methylenedioxyanilino)-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline,
- 6-methoxy-4-(2,3-methylenedioxyanilino)-7-(3-piperidinopropoxy)quinazoline,
- 6-methoxy-4-(2,3-methylenedioxyanilino)-7-(N-methylpiperidin-4-ylmethoxy)quinazoline,
- 7-(2-hydroxy-3-pyrrolidin-1-ylpropoxy)-6-methoxy-4-(2,3-methylenedioxyanilino)-quinazoline,
- 10 7-[2-hydroxy-3-(N-isopropyl-N-methylamino)propoxy]-6-methoxy-4-(2,3-methylenedioxyanilino)quinazoline,
- 7-[3-(4-cyanomethylpiperazin-1-yl)-2-hydroxypropoxy]-6-methoxy-4-(2,3-methylenedioxyanilino)quinazoline,
- 6-methoxy-4-(2,3-methylenedioxyanilino)-7-{2-[2-(4-methylpiperazin-1-yl)ethoxy]ethoxy}quinazoline,
- 15 4-(6-chloro-2,3-methylenedioxyanilino)-7-[3-(4-cyanomethylpiperazin-1-yl)propoxy]-6-methoxyquinazoline,
- 4-(6-chloro-2,3-methylenedioxyanilino)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline,
- 4-(6-chloro-2,3-methylenedioxyanilino)-6-methoxy-7-(3-piperidinopropoxy)quinazoline,
- 20 4-(6-bromo-2,3-methylenedioxyanilino)-6-methoxy-7-(3-piperidinopropoxy)quinazoline,
- 6-methoxy-4-(2,3-methylenedioxyanilino)-7-[2-(N-methylpiperidin-4-yl)ethoxy]quinazoline,
- 6-methoxy-4-(2,3-methylenedioxyanilino)-7-[2-(4-pyridyloxy)ethoxy]quinazoline,
- 6-methoxy-4-(2,3-methylenedioxyanilino)-7-(3-pyridylmethoxy)quinazoline,
- 4-(6-chloro-2,3-methylenedioxyanilino)-7-(2-cyanopyrid-4-ylmethoxy)-
- 25 6-methoxyquinazoline and
- 4-(6-chloro-2,3-methylenedioxyanilino)-6-methoxy-7-(N-methylpiperidin-4-ylmethoxy)quinazoline;
- or a pharmaceutically-acceptable acid-addition salt thereof.
- 30 14. A process for the preparation of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, according to claim 1 which comprises :-
- (a) the reaction of a quinazoline of the Formula II



II

wherein L is a displaceable group and m and R¹ have any of the meanings defined in claim 1 except that any functional group is protected if necessary, with an aniline of the Formula III



III

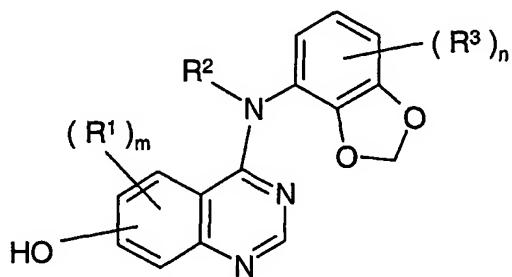
5 wherein R², n and R³ have any of the meanings defined in claim 1 except that any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means;

(b) for the production of those compounds of the Formula I wherein at least one R¹ group is a group of the formula

10

Q¹-X¹

wherein Q¹ is an aryl-(1-6C)alkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl-(1-6C)alkyl or heterocyclyl-(1-6C)alkyl group or an optionally substituted alkyl group and X¹ is an oxygen atom, the coupling of a quinazoline of the Formula V



V

15

wherein m, R¹, R², n and R³ have any of the meanings defined in claim 1 except that any functional group is protected if necessary, with an appropriate alcohol wherein any functional group is protected if necessary whereafter any protecting group that is present is removed by conventional means;

20

(c) for the production of those compounds of the Formula I wherein R¹ is an

amino-substituted (1-6C)alkoxy group, the reaction of a compound of the Formula I wherein R¹ is a halogeno-substituted (1-6C)alkoxy group with a heterocyclyl compound or an appropriate amine;

(d) for the production of those compounds of the Formula I wherein R¹ is a hydroxy group, the cleavage of a quinazoline derivative of the Formula I wherein R¹ is a (1-6C)alkoxy or arylmethoxy group;

(e) for the production of those compounds of the Formula I wherein an R¹ group contains a primary or secondary amino group, the cleavage of the corresponding compound of the Formula I wherein the R¹ group contains a protected primary or secondary amino group;

(f) for the production of those compounds of the Formula I wherein an R¹ group contains a (1-6C)alkoxy or substituted (1-6C)alkoxy group or a (1-6C)alkylamino or substituted (1-6C)alkylamino group, the alkylation of a quinazoline derivative of the formula I wherein the R¹ group contains a hydroxy group or a primary or secondary amino group as appropriate;

(g) for the production of those compounds of the Formula I wherein R¹ is an amino-hydroxy-disubstituted (1-6C)alkoxy group, the reaction of a compound of the Formula I wherein the R¹ group contains an epoxy-substituted (1-6C)alkoxy group with a heterocyclyl compound or an appropriate amine; or

(h) for the production of those compounds of the Formula I wherein an R¹ group contains a hydroxy group, the cleavage of the corresponding compound of the Formula I wherein the R¹ group contains a protected hydroxy group;

and when a pharmaceutically-acceptable salt of a quinazoline derivative of the Formula I is required it may be obtained using a conventional procedure.

15. A pharmaceutical composition which comprises a quinazoline derivative of the
25 Formula I, or a pharmaceutically-acceptable thereof, as defined in claim 1 in association with
a pharmaceutically-acceptable diluent or carrier.

16. A quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt
thereof, as defined in claim 1 for use in a method of treatment of the human or animal body by
30 therapy.

17. The use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined in claim 1 in the manufacture of a medicament for use as an anti-invasive agent in the containment and/or treatment of solid tumour disease.

INTERNATIONAL SEARCH REPORT

I	nternational Application No
PCT/GB 01/03649	

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D405/12 C07D405/14 A61K31/517 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 607 439 A (EISAI) 27 July 1994 (1994-07-27) page 0; claims; tables 7-12,34-58 -----	1,14,15
A	WO 98 13354 A (ZENECA) 2 April 1998 (1998-04-02) page 51 -page 54; claims -----	1,14,15, 17
A	WO 97 38994 A (ZENECA) 23 October 1997 (1997-10-23) claims 1,7; examples 1-7 -----	1,14,15, 17

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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Date of the actual completion of the international search

Date of mailing of the international search report

7 November 2001

14/11/2001

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INTERNATIONAL SEARCH REPORT

Information on patent family members

National Application No

PCT/GB 01/03649

Patent document cited in search report		Publication date	Patent family member(s)	Publication date	
EP 607439	A	27-07-1994	AU 668363 B2 AU 2685192 A EP 0607439 A1 FI 941417 A KR 138695 B1 NO 941101 A US 5576322 A CA 2116336 A1 CN 1071164 A HU 70854 A2 WO 9307124 A1 JP 3081172 B2 JP 10095776 A JP 2818487 B2 JP 2000264877 A JP 2000273089 A JP 2000264885 A MX 9205542 A1 NZ 244526 A PT 100905 A US 5693652 A US 5801180 A ZA 9207465 A		02-05-1996 03-05-1993 27-07-1994 25-03-1994 01-10-1998 30-05-1994 19-11-1996 15-04-1993 21-04-1993 28-11-1995 15-04-1993 28-08-2000 14-04-1998 30-10-1998 26-09-2000 03-10-2000 26-09-2000 31-03-1993 26-07-1995 28-02-1994 02-12-1997 01-09-1998 13-04-1993
WO 9813354	A	02-04-1998	AU 729968 B2 AU 4561397 A BR 9711302 A CN 1231662 A CZ 9901039 A3 EP 0929530 A1 WO 9813354 A1 JP 2001500891 T NO 991422 A PL 332385 A1 SK 38999 A3 TR 9900674 T2 HU 9902850 A2		15-02-2001 17-04-1998 17-08-1999 13-10-1999 16-06-1999 21-07-1999 02-04-1998 23-01-2001 24-03-1999 13-09-1999 08-10-1999 21-07-1999 28-04-2000
WO 9738994	A	23-10-1997	AU 2303097 A DE 69706292 D1 EP 0892799 A1 WO 9738994 A1 US 5770603 A		07-11-1997 27-09-2001 27-01-1999 23-10-1997 23-06-1998